Impact of Gastrointestinal Disease States on Oral Drug Absorption – implications for formulation design – a PEARRL review

Angela Effinger[1], Caitriona M. O'Driscoll[2], Mark McAllister[3], Nikoletta Fotaki[1]*

[1] Department of Pharmacy and Pharmacology, University of Bath, Bath, UK

[2] School of Pharmacy, University College Cork, Cork, Ireland

[3] Pfizer Drug Product Design, Sandwich, UK

Address for correspondence:

Dr Nikoletta Fotaki

Department of Pharmacy and Pharmacology

University of Bath

Claverton Down

Bath, BA2 7AY

United Kingdom

Tel. +44 1225 386728

Fax: +44 1225 386114

E-mail: n.fotaki@bath.ac.uk

Contents

1. Introduction 5
2. Physiological alterations in GI diseases affecting absorption 6
2.1. Inflammatory bowel diseases 6
2.1.1. General information 6
2.1.1.1. Ulcerative colitis 6
2.1.1.2. Crohn's disease 7
2.1.2. Gastrointestinal transit time/motility and pH 7
2.1.2.1. Ulcerative colitis 7
2.1.2.2. Crohn's disease 10
2.1.3. Composition of luminal contents 11
2.1.3.1. Ulcerative colitis 11
2.1.3.2. Crohn's disease 12
2.1.4. Permeation and transport systems 13
2.1.4.1. Ulcerative colitis 13
2.1.4.2. Crohn's disease 14
2.1.5. Metabolism 15
2.1.5.1. Ulcerative colitis 15
2.1.5.2. Crohn's disease 15
2.1.6. Microbiota 16
2.1.6.1. Ulcerative colitis 18
2.1.6.2. Crohn's disease 18
2.2. Celiac disease 18
2.2.1. General information 18
2.2.2. Gastrointestinal transit time/motility and pH 19
2.2.3. Composition of luminal contents 20
2.2.4. Permeation and transport systems 20
2.2.5. Metabolism 21
2.2.6. Microbiota 21
2.3. Irritable bowel syndrome 21
2.3.1. General information 21
2.3.2. Gastrointestinal transit time/motility and pH 22
2.3.3. Composition of luminal contents 22
2.3.4. Permeation 22
2.3.5. Microbiota 23

2.4. Short Bowel Syndrome 23
2.4.1. General information 23
2.4.2. Gastrointestinal transit time/motility and pH 23
2.4.3. Composition of luminal contents 24
2.4.4. Permeation 25
2.4.5. Microbiota 25
3. Drug-related factors affecting absorption in GI diseases 26
3.1. Molecular weight 26
3.2. Lipophilicity 27
3.3. Degree of ionization 29
4. Formulation-related factors affecting absorption in GI diseases 31
4.1. Immediate-release formulation 31
4.2. Modified-release formulation 32
4.2.1. Time-controlled release 32
4.2.2. pH-controlled release 33
4.3. Azo-bonded prodrug formulations 33
5. Methods to predict drug product performance 34
5.1. In vitro dissolution and release testing 35
5.2. PBPK models 37
6. Conclusion and outlook 38
7. Acknowledgements 39

Abstract

Objectives

Drug product performance in patients with gastrointestinal (GI) diseases can be altered compared to healthy subjects due to pathophysiological changes. In this review relevant differences in patients with inflammatory bowel diseases, celiac disease, irritable bowel syndrome and short bowel syndrome are discussed and possible *in vitro* and *in silico* tools to predict drug product performance in this patient population are assessed.

Key findings

Drug product performance was altered in patients with GI diseases compared to healthy subjects, as assessed in a limited number of studies for some drugs. Underlying causes can be observed pathophysiological alterations such as the differences in GI transit time, the composition of the GI fluids and GI permeability. Additionally, alterations in the abundance of metabolising enzymes and transporter systems were observed. The effect of the GI diseases on each parameter is not always evident as it may depend on the location and the state of the disease. The impact of the pathophysiological change on drug bioavailability depends on the physicochemical characteristics of the drug, the pharmaceutical formulation and drug metabolism. *In vitro* and *in silico* methods to predict drug product performance in patients with GI diseases are currently limited but could be a useful tool to improve drug therapy.

Conclusions

Development of suitable *in vitro* dissolution and *in silico* models for patients with GI diseases can improve their drug therapy. The likeliness of the models to provide accurate predictions depends on the knowledge of pathophysiological alterations and thus, further assessment of physiological differences is essential.

1. Introduction

Oral drug absorption is a very complex process which is dependent on the physiological conditions in the gastrointestinal (GI) tract, the pharmaceutical formulation and the physicochemical characteristics of the drug. [1] Pharmacokinetic properties of drugs often display high variability in a healthy population group and pathophysiological changes in patients with GI diseases can further intensify this variability and affect drug product performance. [2]

Patients suffering from GI diseases take a variety of medicines not only for the GI condition but also for concomitant conditions. Differences in the bioavailability of drugs due to the GI disease state can provoke sub-therapeutic or toxic levels of drugs and therefore, have an impact on the safety and efficacy of drug therapy. [3]

Differences in the pharmacokinetics of orally administered drugs between healthy subjects (controls) and patients with GI diseases have been observed .[4; 5] Careful interpretation is needed, as some of these studies are poorly controlled, include only a small patient population and study findings are conflicting. Various physiological factors affecting drug absorption can be altered in GI disease states. Differences in GI transit time and hydrodynamics influence the passage of the drug and formulation through the GI compartments.[6; 7] Changes in the composition and characteristics of GI fluids such as bile salt concentrations, pH and osmolality can affect the drug release from formulations and the solubilisation of the drug.[8] Alterations of the GI membranes and dissimilar expression of transporter systems can affect drug permeability.[9] Differences in the expression pattern of metabolic enzymes in the GI membrane can influence the intestinal first pass metabolism.[8] Alterations in the composition and the location of the GI microbiota can change the exposure of drugs and formulations to bacterial enzymes and may therefore change the metabolism or release of the drug respectively.[10; 11]

To enable prediction of the *in vivo* performance of drug products in healthy adults the use of *in vitro* dissolution methods and *in silico* models has been established.[12; 13] Knowledge of the pathophysiological GI conditions can improve the design of *in vitro* and *in silico* models, improve the ability to predict the drug product performance in patients with GI diseases and facilitate the development of suitable formulations to enhance drug efficacy.

The current review gives an overview of altered GI conditions in patients with inflammatory bowel disease (IBD), celiac disease, irritable bowel syndrome (IBS) and short bowel syndrome (SBS). The consequences of these disease states on drug absorption are analysed. Finally, the suitability of existing *in vitro* dissolution and *in silico* models to predict the drug product performance in patients with GI diseases is critically discussed.

2. Physiological alterations in GI diseases affecting absorption

2.1. Inflammatory bowel diseases

2.1.1. General information

IBD is a recurrent or continuous inflammation of the bowel. Numerous factors (environmental, microbial and genetic) contribute to IBD while its aetiology remains still unknown.[14] In the US 1.4 million people suffer from IBD and 396 per 100 000 persons worldwide.[8] The prevalence of IBD is constantly rising. It is higher in northern, industrialized countries and emerges in newly industrialized countries.[15; 16] The two main forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). Numerous alterations in the GI physiology of IBD patients (e.g. mucosal lesions, thickened bowel wall and strictures) may influence drug absorption.[17]

2.1.1.1. Ulcerative colitis

UC is a continuous uniform inflammation of the colon and rectum with periods of relapse and remission. Typically, the inflammation spreads from the rectum/ descending colon to the

acending colon. Depending on the affected area and extent of the disease it can be grouped into ulcerative proctitis, left-side colitis, sub-total colitis and pancolitis.[18] The diffuse inflammation involves only the mucosa and submucosa which appear granular and haemorrhagic. During active disease UC histology reveals neutrophil-mediated damaged epithelium.[19] This includes cryptitis, crypt abscesses where the lumen is filled with neutrophils and debris, and mucosal ulceration.[19] As the disease progresses, neutrophils infiltrate the lamina propria, crypts get shorter and branched and Paneth cells occur in the left colon.[19] The typical clinical manifestation of UC includes chronic diarrhoea with blood in the stool.[20]

2.1.1.2. Crohn's disease

The second type of IBD is CD. CD can affect the entire GI tract from mouth to anus, often discontinously, but is most likely to occur in the terminal ileum or ascending colon.[21] Initially the disease is limited to the submucosa which appears red and swollen due to lymphoid hyperplasia and lymphedema.[22] In a later stage, the disease extends transmurally and involves the full thickness of the GI wall.[21; 22] Endoscopic examination of CD patients reveals cobble-stoning mucosa and linear or aphthous ulcers with a haemorrhagic rim form. Radiological findings in CD typically illustrate ileac involvement, fistulas and asymmetric manifestation. The classic clinical presentation of CD involves diarrhoea and recurrent abdominal pain. Other symptoms include abdominal cramps, fever, malaise and weight loss. CD complications include malabsorption, bowel obstruction, strictures, crypt abscesses and fistulas.[22]

2.1.2. Gastrointestinal transit time/motility and pH

2.1.2.1. Ulcerative colitis

GI transit time varies between healthy adults and patients with ulcerative colitis (Table 1). Different results considering the total gastrointestinal transit time (TGTT) have been

published. TGTT was strongly increased in patients with UC and this finding was even more pronounced in patients in remission compared to patients with severe disease.[23; 24] Similar TGTT to controls has been observed in one study possibly attributed to the methodology (large size of the telemetery capsule).[25] UC patients with severe disease have shown high variability in TGTT.[26]

Gastric residence time in the fed state was slightly prolonged in UC patients but this was not statistically significant.[23; 27] In the fasted state, patients with UC have shown similar gastric residence times as controls.[26] Small intestinal transit times were slightly prolonged (0.2h-1.3h) in UC patients compared to controls as confirmed by a prolonged orocecal transit time as monitored using the lactulose breath test.[23; 24; 27-30]

Colonic transit times measured with a telemetry capsule were increased in patients with UC, mainly due to a prolonged residence time in the middle and distal colon.[23; 28] However, decreased colonic transit times were also observed which could be attributed to the mild disease state.[27] The range of colonic transit times in healthy volunteers is 7h to 20h whereas a much wider range (2h to 97.7h) was observed for patients with very active UC consistent with high variability in the disease state.[13; 26]

GI motility in the jejunum and ileum as quantified by Magnetic Resonance Imaging (MRI) was not altered in patients with UC compared to controls.[34] After the intake of a meal, the colonic motility in patients with UC in remission was similar to controls.[35] Whereas the low-amplitude propagating contractions in the colon responsible for the transport of liquid contents and gases were found more often in UC patients in remission than in controls, the amount of high-amplitude propagating contractions which mainly transport solid contents was similar to controls.[35]

The pH profile in patients with UC was investigated in several studies (Figure 1).[25-28; 36-38] In the stomach pH was slightly higher and no major pH changes in the small intestine were observed in patients with UC compared to healthy subjects. Only the time to reach a pH of 7 in the small bowel was prolonged in patients with UC compared to controls.[27]

For colonic pH values conflicting results have been published (Table 2). A decrease in colonic pH was mainly observed apart from two studies in which similar or even higher pH values were detected possibly due to the individual form of the disease, the status of the inflammation process and the current treatment of the patients.

2.1.2.2. Crohn's disease

An overview over the studies investigating GI transit time in CD is given in Table 3. Gastric emptying times in patients with CD in the fed state were prolonged as measured by scintigraphy of a capsule containing ^{111}In-labelled pellets.[40] In the fasted state, gastric emptying times in CD patients were similar to patients with different diagnosis using small capsule endoscopy studies.[40; 41] Small intestinal transit times were prolonged when measured with small capsule endoscopy studies but similar when measured by scintigraphy of labelled pellets and thus, the GI passage could be altered according to the pharmaceutical dosage form.[30; 40; 41] This finding could also be attributed to the disease state as a recent study showed that CD patients with active disease have an increased small intestinal transit time while patients with inactive disease showed similar small intestinal transit times compared to non-IBD patients.[30] Orocecal transit times were prolonged in CD patients.[29; 42] The passage through the ascending colon was not significantly different but high disease activity was linked to a shorter transit time.[40]

Jejunal and ileac motility in patients with CD were similar to controls whereas terminal ileum motility was decreased.[34] Differences in bowel hydrodynamics could occur due to the thickened bowel wall in CD and as a result of strictures which hinder the passage of gastrointesinal fluids.[17]

The pH profile in patients with CD was investigated in several studies (Figure 2).[25; 36; 43; 44] Patients with CD showed a tendency to higher pH in the stomach compared to controls which correlated with decreased gastric acid secretion especially when patients were malnourished (mean basal acid output: 0.64mEq/h (0.33) (malnourished), 2.12mEq/h (0.88) (nutritional support) vs. 3.85mEq/h (0.93) in controls, maximal acid output: 7.36mEq/h (1.38) (malnourished), 12.76mEq/h (2.50) (nutritional support) vs. 25.53mEq/h (4.58) in controls).[25; 35; 45] Mean or median pH values in the small intestine of patients with CD were similar

compared to controls whereas the observed pH range was higher in CD patients. Similar results with more fluctuations were found for colonic pH values in CD patients with the exemption of one study with an overall mean decreased colonic pH (5.3 vs. 6.8).[25; 36; 43]

2.1.3. Composition of luminal contents

2.1.3.1. Ulcerative colitis

The composition of the ascending colon fluid in the fasted state in UC patients in relapse and remission differed from healthy adults with elevated concentrations of soluble proteins (relapse: 18.9mg/ml (8.1), remission: 19.0mg/ml (10.8), healthy: 9.8mg/ml (4.6)) in contrast no difference in soluble carbohydrates was observed (relapse: 5.4mg/ml (2.7), remission: 6.4mg/ml (4.1), healthy: 8.1mg/ml (8.6)).[37] Phosphatidylcholine, an essential constituent for the normal mucus barrier function, was strongly decreased in the colonic mucus barrier of patients with UC (-70%) [as measured by mass spectrometric analysis of lipid extracts of specimens of rectal mucus]. Beneficial effects were shown when phosphatidylcholine was used as a treatment option for UC.[47-49] Due to the low number of subjects only a trend to lower concentrations of phosphatidylcholine could be observed in the ascending colon fluids of UC patients in relapse (0.31mM) or remission (0.30mM) in the fasted state compared to controls (0.36mM).[37; 39] The faecal fluids of patients with UC were found to have a lower concentration of potassium (33.0mmol/l vs. 84mmol/l) and a higher concentration of sodium (67.8mmol/l vs. 34mmol/l) and chloride (53.1mmol/l vs. 18.5mmol/l) compared to healthy subjects.[50]

Regarding the properties of the ascending colon fluid of patients with UC, both the volume and surface tension were similar compared to controls (relapse: 26.8ml (13.5), remission: 21.2ml (8.8), controls: 22.3ml (7.7) and relapse: 41.6mN/m (3.1), remission: 40.6mN/m (3.4), controls: 39.2mN/m).[37] The buffer capacity of the ascending colon fluid in remission and

relapse were similar but higher than in controls (with hydrochloric acid relapse: 32.0mmol/l/ΔpH (18.1), remission: 37.7mmol/l/ΔpH (15.4), controls: 21.4mmol/l/ΔpH (7.9); with sodium hydroxide solution: relapse: 18.3mmol/l/ΔpH (10.4), remission: 16.7mmol/l/ΔpH (5.8), controls: 10.3mmol/l/ΔpH).[37] Osmolality values were higher in patients with UC in relapse (199.6±127.4mOsmol/kg) and remission (290.1±165.6mOsmol/kg) compared to controls (80.6±102.5mOsmol/kg).[37] Faecal fluid osmolality was similar to controls (341.1mOsm/kg vs. 348.5mOsm/kg).[50]

2.1.3.2. Crohn's disease

The composition of GI fluids in patients with Crohn's disease has not been described. The bile acid pool size (weight of total bile acids) was decreased to only 38-58% in patients with CD compared to controls as measured by induced gall bladder evacuation, subsequent aspiration of the duodenal fluid and analysis of labelled bile acid (previously administered) vs. total bile acid concentrations.[51-53] It has been reported that >90% of patients with resected CD and 11-52% of patients with unresected CD suffer from bile acid malabsorption.[54] As a consequence, postprandial duodenal bile acid concentrations were decreased in 9 of 19 CD patients with a mean value of 6.04mM (3.92).[55] The failure in the reabsorption of bile acids is a result of the disease localisation in the ileum, as the ileac sodium/bile acid cotransporter is responsible for the active reabsorption of the conjugated bile acids. As a consequence, bile acid malabsorption is particularly severe in CD patients after resection of the distal ileum.[56]

With regard to the properties of the GI fluids, faecal fluid osmolality in CD patients was increased (132-152%) as observed in two studies.[50; 57]

Changes in the exocrine pancreatic function have also been reported in CD. A significant decrease of amylase (33-85%), trypsin (29%) and lipase (28-80%) activity in the fed state in

the duodenum of CD patients compared to controls was observed which was particularily strong in malnourished patients.[45; 58; 59]

2.1.4. Permeation and transport systems

Transporters in the GI tract can increase drug bioavailability by transferring drugs from the luminal to the basolateral site (uptake transporters) or decrease drug absorption by transport in opposite direction (efflux transporters).

For uptake transporters, differences in the transporter expression have been reported in IBD. The expression of OCTN1 and OCTN2, transporters for cationic drugs, is downregulated in UC patients and IBD patients were found to have mutations in the genes encoding their expression.[60; 61] The expression of PepT1, an important influx transporter for peptidomimetics, is upregulated in the colon in chronic inflammation associated with IBD, with no information being available for its expression in the small intestine of these patients.[61] In healthy adults PepT1 is majorly expressed in the small intestine and only very low amounts of PepT1 are expressed in the colon.[61] Therefore, alterations in the colonic expression pattern of PepT1 may have only limited influence on drug absorption of peptidomimetics such as β-lactam antibiotics and angiotensin-converting enzyme inhibitors.

2.1.4.1. Ulcerative colitis

The composition of the gastrointesinal membranes can be altered by GI diseases and thus, influence drug permeation. The thickness of the colonic and rectal mucus layer was reduced in UC patients compared to controls which was more pronounced in distal regions (right colon: 90(79) vs. 107(48)µm, left colon: 43µm (45) vs. 134µm (68), rectum: 60µm (86) vs. 155µm (54)).[62]

The efflux transporters, P-glycoprotein(P-gp), BCRP and MRP2 are the most important efflux transporters in the luminal membrane of the small intestine and they act by limiting cellular

uptake into the enterocyte and enhancing the excretion of xenobiotics.[63] The expression levels of BCRP, MRP2 and P-gp in the colonic and rectal mucosa of UC patients are strongly decreased during active inflammation.[64] In contrast, elevated levels of P-gp in the colon of UC patients were found in another study possibly due to a milder disease state in the study subjects.[64] The bioavailability of sulfasalazine, a substrate of MRP2 and BCRP and prescribed for IBD, could thus be increased in UC and produce more side effects.[61]

2.1.4.2. Crohn's disease

The thickness of the colonic and rectal mucus layer was increased in CD patients compared to controls (right colon: 190(83) vs. 107(48)µm, left colon: 232(40) vs. 134(68)µm, rectum: 294(45) vs. 155(54)µm).[62]

Baseline permeability in surgical specimens from the distal ileum of CD patients was similar compared to colon cancer patients as measured by permeability to ^{51}Cr-EDTA and electrical resistance in Ussing chambers.[66] However, after exposure to sodium caprate, a stimulus to the luminal epithelium, the increase in paracellular permeability in CD was more pronounced.[66] This hyper responsiveness might be of particular interest because certain drugs may act as luminal stimulus.

Paracellular permeability for various compounds like 51Cr-EDTA, [99mTc]DTPA, sucrose and lactulose was increased in patients with CD compared to controls probably caused by the opening of tight junctions.[67-70]

Transcellular permeability, as indicated by mannitol's permeability in *in vivo* lactulose/mannitol intestinal permeability studies, was not altered in CD patients compared to controls.[71; 72] Mannitol is absorbed via the paracellular pathway in *in vitro* permeability studies (e.g. Ussing chambers), whereas in *in vivo* intestinal permeability studies it is used as marker

for the transcellular route due to a solvent drag effect caused by the hyperosmolality of villus tips.[73]

Active transport systems can also be altered in CD. The expression of P-gp was increased to over 200% in the duodenal biopsy specimens and in the colon of CD patients.[65; 74] This increased P-gp expression could be responsible for the decreased absorption of tacrolimus and justify the higher doses of tacrolimus required in a patient with CD.[74]

2.1.5. Metabolism

2.1.5.1. Ulcerative colitis

The expression of metabolizing enzymes in the large intestine of patients with UC is altered compared to controls. In colorectal tissue the expression of the most abundant metabolizing enzyme, CYP3A4, was slightly elevated (125%) but the expression of CYP2C9, CYP1A1 and UDP-glucuronic acid transferase was decreased in enterocytes (74%, 81%, 72%).[65] In biopsy samples of the terminal ileum and various regions of the colon the expression of CYP3A and CYP2D6 was not altered but the expression of CYP1A1 was increased.[75] Whereas in the terminal ileum and colon no difference in CYP2E1 expression compared to controls was observed, one study found increased expression (137%) in colorectal tissue probably due to the inflammation processes in active disease.[65; 75]

Considering conjugation reactions, sulphation by sulfotransferases in the colonic mucosa of UC patients was reduced to <15% compared to controls.[76] The systemic sulphation pathway is not reduced as shown by no alteration in paracetamol metabolism in UC patients.[77]

2.1.5.2. Crohn's disease

Patients with CD displayed different expression patterns for metabolizing enzymes. The expression of CYP3A4 was more than doubled in the colon of CD patients compared to controls and also increased, together with CYP3A5 expression, in duodenal biopsies of

children with CD.[65; 78] This may alter the bioavailability of substrates for both enzymes such as corticosteroids. In a recent study, lower CYP3A4 activity was shown in patients with CD as assessed after intravenous and oral administration of midazolam (CYP3A4 substrate).[79] This finding was mainly attributed to a lower hepatic CYP3A4 activity (hepatic extraction ratio in CD patients 0.11 vs. 0.36-0.62 in healthy subjects; intestinal extraction ratio in CD patients 0.64 vs. 0.30-0.61 in healthy subjects). Furthermore, in the same study the 25% of the variability in budesonide pharmacokinetics (CYP3A4 substrate) was attributed to the reduced CYP3A4 activity.

Elevated expression of other metabolizing enzymes like CYP2C9 (130%), CYP1A1 (134%) and UDP-glucuronic acid transferase (135%) was also observed.[65; 75] CYP2B6 levels were augmented to 178% in CD patients and the expression of glutathione-S-transferase was strongly raised (159-167%).[65] A tendency to increased levels of CYP2E1 (122%) was reported.[64; 74] CYP3A and CYP2D6 expression was similar to controls.[75]

2.1.6. Microbiota

In recent years, the importance of the GI microbiota in IBD patients is increasingly recognised. At the early stages of IBD differences in the microbiota (dysbiosis) are already present and the role in disease etiology and disease progression is currently being investigated.[80] The emergence of several new methodologies (metagenomic sequencing, transcriptomics and metabolomics) in the last years has provided information on bacterial functions over and above the broad taxonomic profiles.[80] The microbiota of patients with IBD was decreased in diversity, as the gene catalogue of the human gut microbiome in IBD patients showed 25% less bacterial genes compared to controls, with a shift to more potentially inflammatory and less potentially protective bacterial species.[80; 81] Reduced amounts of Faecalibacteria,

371 Leuconostocaceae, *Odoribacter splanchnius*, *Phascolarctobacterium* and *Roseburia* in IBD
372 patients led to decreased levels of short chain fatty acids (SCFA) which are involved in immune
373 regulatory functions and stimulate bile acid production and mucosal protection.[80; 82-84] Several
374 drugs are processed by bacterial enzymatic action which is possibly affected by the altered
375 composition of the microbiota observed in IBD (Table 4).

2.1.6.1. Ulcerative colitis

The microbiota of UC patients was richer in Proteobacteria, Bacteroides, Fusobacteria and Enterobacteriaceae compared to controls.[89] Decreased levels of *Faecalibacterium prausnitzii*, *Bacteroides fragillis, Ruminococcus albus, Roseburia intestinalis, Clostridium coccoides, Eubacterium rectale*, enterohepatic *Helicobacter* species and the *Clostridium leptum* group were observed.[89]

Small intestinal bacterial overgrowth (SIBO) was slightly more prevalent in UC patients compared to controls (17.8 % vs. 0.86%).[29] In terms of enyzmatic bacterial function, differences in the colonic mucus of patients with UC were observed. Proteinase activity (657.6units h-1mg dry wt.-1 (150.6) vs. 77.2units h-1mg dry wt.-1 (25.9)) and non-specific esterase activity (39.8µmol h-1 mg dry wt.-1 (3.3) vs. 33.9µmol h-1 mg dry wt.-1 (3.7)) were increased compared to controls.[90]

2.1.6.2. Crohn's disease

Changes in bacteria species colonizing the intestine of CD patients were observed with higher amounts of Bacteroidetes and Enterobacteriaceae, specifically *Eschericia coli*, and lower amounts of Firmicutes and *Faecalibacterium prausnitzii* compared to healthy subjects.[91]

45.2% of patients with CD suffered from SIBO compared to only 0.86% of controls.[29] With regard to bacterial enzyme activity, decreased faecal azoreductase activity (11.39mU/g vs. 51.13mU/g), extremely high proteinase activity (585.8units h^{-1}mg dry $wt.^{-1}$ (202.1) vs. 77.2units h^{-1}mg dry $wt.^{-1}$ (25.9)) and elevated non-specific esterase activity (51.7µmol h^{-1} mg dry $wt.^{-1}$ (19.7) vs. 33.9µmol h^{-1} mg dry $wt.^{-1}$ (3.7)) were observed in CD.[85; 90]

2.2. Celiac disease

2.2.1. General information

Celiac disease, affecting 1% of the population, is a genetic autoimmune enteropathy with a hypersensitivity of the patient to gluten.[92; 93] A small intestinal biopsy which shows villous atrophy, crypt hyperplasia and intraepithelial lymphocytosis serves as an additional diagnostic criteria.[93] Normally, the villous atrophy, occurs in patches and is localized at the duodenal bulb and in the descending duodenum but more distal GI segments can also be affected. The villous atrophy results in decreased availability of absorptive surface area leading to impaired drug and nutrient absorption.[94]

2.2.2. Gastrointestinal transit time/motility and pH

The mouth-to-cecum transit time in untreated patients with celiac disease was prolonged compared to controls using the lactulose breath test but significantly decreased after treatment with a gluten-free diet (Table 5).[95-97] Gastric emptying time measured with ^{13}C-octanoic acid breath test and ultrasonographic emptying studies in untreated patients with celiac disease was increased but normalized after treatment with a gluten-free diet.[92; 98; 99] However, with another methodology (small bowel PillCam®) gastric emptying was found to be similar to controls.[98] No alteration of small intestinal transit time was found in celiac disease patients. The faster mean colonic transit time, as measured in one study (n=40) only, was attributed to a subpopulation of patients with very fast colonic transit.[97]

Motility changes in celiac disease patients compared to controls were observed with increased oesophageal motility disturbances.[101]

With regard to the pH profile in patients with celiac disease, a higher jejunal surface pH value with a pH of 6.42 (0.06) or 6.56 (0.14) in untreated patients, 6.32 (0.07) or 6.19 (0.09) in treated patients compared to 5.96 (0.05) or 5.93 (0.05) in controls was observed which might favour the absorption of weakly basic drugs.[102; 103] Intraluminal pH measurements confirmed a higher pH in the proximal small bowel and showed similar pH values in the stomach.[104]

2.2.3. Composition of luminal contents

The composition of GI fluids in patients with celiac disease has not been described. About 20% of patients with untreated celiac disease showed a decreased secretion of at least one pancreatic enzyme.[105] Reduced cholecystokinin secretion as response to a meal, which was observed in celiac disease patients, could lead to decreased gall-bladder motility and small intestinal transit time.[106] This could further provoke an increase and stasis of the bile acid pool.[106; 107] Additionally, increased biliary outputs of phospholipids (0.26mg/kg*h (0.05) vs. 0.08mg/kg*h (0.02)), cholesterol (0.82mg/kg*h (0.10) vs. 0.43mg/kg*h (0.06)) and bile acids (9.28mg/kg*h (1.65) vs. 4.64mg/kg*h (0.45)) were all observed in celiac disease patients.[108]

Protein concentrations in jejunal perfusion fluids were altered in celiac disease patients compared to controls. The concentration of glycosaminoglycan hyaluronan, a connective membrane component, was increased two-fold in the basal state of celiac disease compared to controls.[109] After provoking an immune response by challenging the jejunal segment with gliadin (protein present in wheat), concentrations of albumin and glycosaminoglycan hyaluronan increased up to two-fold indicating increased protein leakage through the GI membrane.[109]

2.2.4. Permeation and transport systems

Differences in paracellular passive diffusion were observed in patients with celiac disease compared to controls with a higher GI permeability of lactulose and ^{51}Cr-EDTA, possibly due to opening of the tight junctions.[71; 110-113]

For the transcellular pathway, a lower permeability for mannitol and polyethylene glycol 400 was observed in *in vivo* intestinal permeability studies, possibly due to the decrease in the absorptive surface area.[110-113]

In the case of efflux transporters, the expression of P-gp in untreated and treated children with celiac disease was elevated compared to controls whereupon gluten withdrawal resulted in a further increase.[114]

2.2.5. Metabolism

Jejunal morphological changes like flattened villi in celiac disease were accompanied by different activity of metabolic enzymes. The CYP3A activity was decreased in patients with celiac disease but treatment with a gluten-free diet subsequently resulted in increased activity.[115] Accordingly, the expression and activity of CYP3A4 in children with celiac disease was reduced.[116]

2.2.6. Microbiota

The microbiota of celiac disease patients was found to be rich in potentially pathogenic gram-negative bacteria and poor in species such as *Lactobacilli* and *Bifidobacteria* compared to controls.[117] After treatment with a gluten-free diet the microbiota shifted to more beneficial species.[117] The prevalence of SIBO in celiac disease patients is not evident due to the heterogeneity of studies (differences in inclusion criteria, no homogeneous controls groups, low study quality), whereas SIBO prevalence appears to be higher in patients with celiac disease patients with persisting symptoms following withdrawal of gluten.[118-121]

2.3. Irritable bowel syndrome

2.3.1. General information

Irritable bowel syndrome (IBS) is a chronic GI disorder, prevalent in 5-11% of the population in most countries, with symptoms such as recurring abdominal pain, bloating and changes in the pattern of bowel movements.[122] The disease can either be predominated by diarrhoea (IBS-D) or constipation (IBS-C) or it can be a combination of both (IBS-M). The recrudescence of the symptoms is often linked with psychological stress.

2.3.2. Gastrointestinal transit time/motility and pH

Gastric emptying time and small intestinal transit time were not significantly different in IBS patients compared to controls measured with a SmartPill GI monitoring system (51.23min (59.1) vs. 76.81min (73.2) and 218.56min (59.60) vs. 199.20min (82.31)).[123] Differentiation between IBS subtypes, revealed that small bowel transit time and total GI transit time were shorter in IBS-D patients (3.3h (0.3) vs. 4.2h (0.2) and 35h (5) vs. 53h (4)) and prolonged in IBS-C patients (5.4h (0.3) vs. 4.2h (0.2) and 87h (13) vs. 53h (4)).[124]

The pH profile in IBS patients in the fasted state was similar to controls throughout the four quartiles of the small intestine indicating no alteration in the ionization of administered drugs compared to controls.[123]

2.3.3. Composition of luminal contents

The composition of GI fluids in patients with IBS has not been described. Around 32% of IBS patients suffer from moderate bile acid malabsorption with a 10% prevalence of severe bile acid malabsorption.[125] Patients with IBS-D, showing a decreased bile acid deconjugation activity in the faeces, have increased levels of faecal primary bile acids, chenodeoxycholic acid, sulphated bile acids and ursodeoxycholic acid and decreased levels of faecal secondary bile acids.[126] Bile acid deconjugation activity was also decreased in the faeces of IBS-C patients.[126]

2.3.4. Permeation

Not all patients with IBS showed an increase in intestinal permeability but for the subgroup of IBS-D patients a higher intestinal permeability was observed more frequently.[127] Rectal permeability tests in patients with IBS-D observed that the passage of macromolecular compounds through rectal biopsies was increased.[128]

2.3.5. Microbiota

The GI microbiota of patients with IBS has been analysed in several studies but inconsistent results have been published due to the lack of differentiation between disease subtypes, the pathophysiology of the disease and the methods used. Patients with IBS had a higher amount of mucosa-associated bacteria at the rectal epithelium than healthy controls.[129] The faecal microbiota was reduced in the *Clostridium coccoides* subgroup and the *Bifidobacterium catenulatum* group and a high ratio of Firmicutes to Bacteroidetes was found in a subgroup of IBS patients.[130-132] The IBS-D subtype could be distinguished by decreased levels of *Lactobacillus spp.*, Bifidobacteria and increased levels of *Escherichia coli*.[126; 129; 132] The microbiota of IBS-C patients was richer in *Bacteroides, Veillonella* spp. and *Bifidobacterium*.[126; 132]

2.4. Short Bowel Syndrome

2.4.1. General information

Short bowel syndrome (SBS) is a malabsorption disorder as a result of the loss of a large part of the bowel due to surgical resection, congenital defects or disease resulting in a remaining intestinal length of less than 200 cm.[133; 134] The diminished intestinal surface area impedes absorption and thus, causes the dehydration and malnutrition with micronutrients and macronutrients of SBS patients which cannot always be overcome with enteral supplements.[135; 136] Drug absorption can equally be impaired in SBS patients and for poorly absorbed drugs alternative routes of administration should be considered.[137]

2.4.2. Gastrointestinal transit time/motility and pH

GI transit time in patients with severe SBS was largely decreased impeding nutrient absorption as well as drug absorption.[138] Different GI transit times according to the method used were observed in patients with SBS: 52.5 minutes (lactulose hydrogen breath testing), 967 minutes

(radiopaque markers) and 96.3 minutes (blue food colour to appear in ostomy effluent or stool). Limitations of the methods include that lactulose hydrogen breath testing can only be used in patients with intact ileocecal valve and the much longer transit time with a radiopaque marker indicates that anatomical changes prevent the passage of the marker.[138] Therefore, stagnation of solid oral dosage forms in the GI tract of SBS patients might also occur and result in a different exposure to the absorptive surfaces and increased variability of drug absorption.

The pH profile in the stomach of patients with SBS was similar compared to controls but higher pH values in the small intestine (6.03 vs. 5.39) and right colon (6.7 vs. 5.8) were observed (Figure 3).[44; 139-141]

2.4.3. Composition of luminal contents

Gastric acid hypersecretion, which can be five-fold greater than basal levels in healthy subjects, is often experienced during the acute stage after surgical resection by patients with SBS. [142] This can result in a pH reduction causing the inactivation of GI fluid components such as pancreatic enzymes. Due to adaptation processes the hypersecretion is normalised during the first weeks or month after resection.[143]

Bile acid malabsorption as a result of the removal of parts of the ileum, their main reabsorption area, results in decreased recirculation of bile salts and a spill over of bile salts to the colon.[142] To compensate for the bile acid loss bile salt production is increased in SBS patients, reaching 10 to 20 fold the production of healthy individuals.[144] If the increased production cannot fully compensate the loss, lower amounts of bile acids in the intestine can prevent the solubilisation and absorption of fatty acids as well as of lipophilic drugs.[145] Choleretic diarrhoea, caused by increased levels of bile salts in the colon and the subsequent loss of chloride and water, could also affect colonic transit time.[142]

2.4.4. Permeation

After removal of a large part of the intestine the remnant parts of the bowel undergo a natural adaption process including changes in the expression of membrane transporters in order to improve the absorption of nutrients.[146] Patients with SBS had an increased amount of PepT1 mRNA in the colon 1.5–2.5 years after resection with normalization over time (9.8 ± 5.7 years after resection).[147; 148]

2.4.5. Microbiota

The faecal and mucosa-associated microbiota of patients with SBS was deeply altered compared to controls. It was rich in *Lactobacillus,* resulting in a greater absorption of carbohydrates in SBS patients, and the specific species *Lactobacillus mucosae* was prevalent in most samples of SBS patients while it was not detected in controls. [147] Decreased amounts of *Clostridium leptum*, *Clostridium coccoides*, Bacteroidetes, Firmicutes, *Bifidobacterium* and *Methanobrevibacter smithii* were found in patients with SBS.[134; 149]

Higher risk of SIBO in patients with SBS is a result of the stagnation of intestinal contents, the impairment of the ileocecal valve and the reduction of the terminal ileum which favours bacterial growth in higher parts of the GI tract.[142] As a consequence, deficiencies of fat-soluble vitamins, problems in fat absorption and increased intestinal permeability can occur.[142]

In summary, an overview of the changes affecting drug absorption in GI disease patients compared to controls is given in Figure 4.

3. Drug-related factors affecting absorption in GI diseases

3.1. Molecular weight

The molecular weight (MW) in conjunction with other physicochemical characteristics such as the charge of the molecule, its hydrophilicity and shape determines the pathway and extent of drug permeability.[150] The rate of diffusion of a drug is inversely proportional to its molecular weight with high molecular weight compounds having low permeability. [150] Molecules with MW<200g/mol can permeate through tight junctions between intestinal cells via paracellular passive diffusion.[151]

In CD and celiac disease, ruptures of the tight junctions can increase the permeability of larger drugs (MW>200g/mol) via the paracellular route by impairing the sieve effect of the tight junctions (Section 2.1.2.3 and 2.2.3). In celiac disease, the decreased absorptive surface area hinders the absorption of small drugs (MW<200g/mol) via the transcellular pathway, probably resulting in a decreased bioavailability compared to controls as indicated by the decreased permeability of mannitol (Section 2.2.3).

Passive transcellular diffusion is restricted for drugs with MW>500g/mol whereas lipophilic drugs with MW 350±150g/mol can readily permeate through the intestinal membrane. In celiac disease, no correlation between drug absorption of different antibiotics and their molecular weight was observed since sulphamethoxazole (MW 253g/mol) and erythromycin stearate (MW 1018.4g/mol) showed a similar absorption pattern.[152] A possible explanation for this may be that the drugs use different pathways to pass the epithelial membrane.

The bioavailability of methyldopa (MW 211g/mol, BCS class III compound) was significantly increased in celiac disease patients (n=10, C_{max} 5.0µg/ml (2.2) vs. 3.1µg/ml (1.1), AUC 20.5µg $ml^{-1}h$ (9.6) vs. 13.4µg $ml^{-1}h$ (4.9)), without a change in the pharmacological response.[153; 154] It should be noted that the patients were already on treatment (gluten-free diet) and more

pronounced differences could be expected in patients without treatment. Since levodopa is completely absorbed via efficient transepithelial carrier transport and the recovery of methyldopa in urine and feces was not altered in celiac disease patients, increased paracellular permeability might not be relevant and the finding might be attributed to other factors such as decreased renal excretion.[155] In contrast, CD patients (n=5) had lower plasma levels of methyldopa (AUC 8.7µg $ml^{-1}h$ (4.3) vs. 13.4µg $ml^{-1}h$ (4.9)) and a reduction in the pharmacological response (sedation, smaller decrease in systolic blood pressure).[154]

Acetaminophen (BCS class I compound) with a low MW of 151g/mol is partly absorbed via the paracellular pathway.[153; 156] Acetaminophen absorption in patients with celiac disease and CD was delayed (celiac untreated $AUC_{0\text{-}1h}$ 9.0µg min/ml (1.6), celiac treated $AUC_{0\text{-}1h}$ 8.2µg min/ml (2.0), CD 9.3µg min/ml (3.5) vs. controls $AUC_{0\text{-}1h}$ 12.4µg min/ml (3.2)) probably due to delayed gastric emptying but the overall acetaminophen absorption was not impaired as indicated by urinary recovery.[157] In SBS patients, total absorption of acetaminophen was decreased as the drug is absorbed in the jejunum and thus, rectal drug administration should be preferred.[158] It should be noted that the changes in the jejunal morphology due to celiac disease did not impair the overall absorption of acetaminophen.[157]

Tioguanine (MW 167g/mol, log P -0.07) showed highly variable absorption in CD patients possibly due to altered paracellular passive diffusion, with possible implication in treatment. [159] Differences in AUC were 4 to 7-fold and in two patients no tioguanine absorption was observed within 6 hours after oral intake for at least one of three different formulations investigated.[160]

3.2. Lipophilicity

Lipophilicity has a high influence on the bioavailability of a drug by affecting its solubility, permeability and metabolism.[161] Drugs can be classified according to their logP in highly (log

P>3), moderately (log P 1-3) and low (log P<1) lipophilic drugs.[162] For highly lipophilic drugs (log P>3) the dissolution and solubility in the aqueous GI fluids is often the rate limiting factor for drug absorption since only the dissolved part of a drug can permeate through the GI membranes and thus, reach the systemic circulation. Alterations in GI diseases can provoke changes in the bioavailability of lipophilic drugs due to changes in GI transit times, reduced GI volumes leading to non-sink conditions and increased surface tension hindering the wetting of the drug surface. Micellar drug solubilisation can also be affected by decreased concentrations of amphiphilic bile components and a reduction in absorptive surface area limits the permeation of drugs via transcellular passive diffusion.

In CD, decreased amounts of bile acids in the luminal fluids, reduced absorptive surface area depending on the location of the disease, and increased small intestinal transit time can affect the absorption of lipophilic drugs (Section 2.1). In celiac disease, impacting factors are the increased concentrations of bile salts and lecithin, increased orocecal transit time and the highly decreased absorptive surface area (Section 2.2).

In CD patients, a highly lipophilic drug, propranolol (log P 3.48, pKa 9.42), showed a higher bioavailability and increased plasma levels possibly due to prolonged small intestinal transit time. Since propranolol is a highly soluble compound (BCS class I), decreased bile salt concentrations are expected to be only secondary.[163; 164] Further investigations with multiple dosing are needed in order to assess if the increased bioavailability is clinically relevant. It should be noted that conflicting results regarding propranolol absorption in celiac disease patients have been reported with in some cases higher propranolol absorption in celiac disease compared to controls whereas in other cases similar absorption was found.[4; 102; 163; 165; 166] Higher propranolol absorption correlated in one study with a measured higher jejunal surface pH resulting in a higher unionized fraction of propranolol but could also be the result of higher bile salt and phospholipid concentrations or the atropic mucosa favouring the transport of

lipophilic drugs. However, jejunal perfusion showed lower propranolol absorption in the jejunum which was apparently compensated in lower intestinal parts.[166]

For levothyroxine, another highly lipophilic drug (log P 3.51) with a narrow therapeutic index, celiac disease patients needed higher initial doses to maintain a euthyroid state (154µg (65) vs. 106µg (46)), which decreased (111µg) after gluten withdrawal.[167; 168] This could be attributed to the reduced absorptive surface area in the small intestine in celiac disease patients (Section 2.2).

In CD and UC, the absorption of prednisolone (log P 1.62, BCS class I), a moderately lipophilic drug, was delayed possibly due to the increased gastric emptying time.[153; 159;169] In one study overall prednisolone absorption in CD patients was only impaired in patients with extensive disease manifestation in the small bowel, whereas in another study a decreased bioavailability of 0.6 (0.2) compared to 0.86 (0.09) in controls was observed also for CD patients with a different disease localisation.[169; 170] The authors of the first study postulated that the methodology of the latter study might have been more sensitive as it included measurements of serum, urine and stool recovery of prednisolone. Highly variable prednisolone serum levels in CD patients with higher disease activity could be attributed to altered CYP3A4 activity.[171] Surprisingly, prednisolone absorption was not altered in patients with celiac disease where absorptive surface area is reduced due to the villous atrophy.[171; 172]

For drugs with low lipophilicity and high hydrophilicity following paracellular permeability, molecular weight (Section 3.1) and charge (Section 3.3) need to be considered for the evaluation of absorption of these drugs in GI diseases.

3.3. Degree of ionization

The degree of ionization influences both the solubility and the permeability of drugs and subsequently the rate of drug absorption. The degree of ionization is dependent on the drug itself and the pH value of the enclosed GI fluids.

Weak bases are protonated and therefore, more soluble in the more acidic compartments of the GI tract (stomach, proximal small intestine). Subsequent increase in pH, when the drug enters the duodenum, may result in a supersaturated state and enhance drug absorption.[169] The unionized form of a drug permeates more readily through the GI membrane and therefore, drug absorption of weak bases is higher in GI compartments with higher pH. In CD, the pH of the stomach is elevated (Section 2.1.2) and decreased solubilisation of weak bases would be expected.

Weak acids are more soluble in GI compartments with a higher pH due to their ionisation profile, but membrane permeation for the more ionized fraction of the drug is impeded.[174] In celiac disease and SBS, small intestinal pH was higher compared to controls which could possibly increase absorption of weak bases (Section 2).

The absorption of a weak acid, folic acid (pKa 4.7), was decreased in celiac disease patients possibly due to the lower absorptive surface area and the slightly elevated jejunal pH (Section 2.2) and therefore, higher ionized amount of folic acid.[102; 175] Folate is highly absorbed in the more acidic milieu in the duodenum and proximal jejunum since the removal of these parts results in folate deficiency that is commonly observed in celiac disease patients.[176]

For two other weak acids, indomethacin (BCS class II) and acetylsalicylic acid (BCS class I), no effect on overall absorption was observed in patient with celiac disease. Only a faster absorption rate (Celiac disease: t_{max} 0.80h (0.60), controls: t_{max} 1.09h (0.16)) was found for acetylsalicylic acid probably due to faster gastric emptying in the fasted state (Section 2.3.1) or differences in drug permeability.[153; 177] Thus, the slightly higher jejunal pH that might

678 decrease the unionized fraction of the drug available for absorption has no effect on absorption
679 (Section 2.2.1). With acetylsalicylic acid, therapeutic outcomes were achieved in patients with
680 SBS revealing no impairment of drug absorption.[178]

681 4. Formulation-related factors affecting absorption in GI diseases

682 Pharmaceutical formulations are designed to overcome the challenges of the GI tract and to
683 deliver the active pharmaceutical ingredient into the systemic circulation. A variety of different
684 approaches is used to optimize the bioavailability, safety and efficacy of the drug. Enteric-
685 coated formulations protect the drug from gastric acid or the stomach from the toxicity of the
686 drug. Modified-release formulations can ensure constant drug levels, facilitate drug therapy by
687 minimizing the administration frequency and deliver the drug locally to specific compartments
688 of the GI tract. Immediate-release formulations are a simple approach if no further modification
689 of the drug bioavailability is needed. In order to fulfil their purpose, the different formulations
690 are designed based on the conditions of the GI tract in healthy subjects e.g., pH, microbiota
691 and transit time (Section 2). However, these parameters can be altered in patients with GI
692 diseases impacting the drug release/dissolution from the formulation.

693 4.1. Immediate-release formulation

694 For immediate release formulations, the disintegration of the pharmaceutical formulation, the
695 disaggregation of the granules and finally the dissolution of the particles will be affected by
696 the hydrodynamics in the GI tract. Transit times in the different GI compartments, altered by
697 GI diseases (Section 2), affect the time until the absorption site is reached and the time available
698 for absorption. Delayed gastric emptying as observed in CD and untreated celiac disease in the
699 fed state (Section 2) can result in a delayed t_{max} since for most drugs the main absorptive area
700 is the large surface area of the small intestine. Patients with faster gastric emptying may also
701 show a shorter t_{max}.[4] Differences in terms of bile salts as observed in celiac disease, CD and

SBS (Section 2) can affect the wetting of the pharmaceutical formulation and therefore, change the disintegration time.

4.2. Modified-release formulation

4.2.1. Time-controlled release

For the treatment of IBD pharmaceutical formulations with time-controlled release mechanism have been developed to deliver drugs to their target site in the colon. Depending on the transit times in the different compartments of the GI tract the amount of drug available in each compartment may vary for these formulations. For UC a high variability in colonic transit time was observed while in CD passage through the colon was accelerated (Section 2.1.2.1 and 2.1.2.2). Faster colonic transit time can lead to a large amount of drug not being released and therefore, failure of the therapeutic effect may occur.

When a micro pellet formulation of mesalazine coated with ethyl cellulose (Pentasa®,Ferring Pharmaceuticals, Copenhagen, Denmark) was administered to healthy subjects, drug product performance was not affected by a laxative induced diarrhoea.[179; 180] Thus, reduced colonic transit time as observed in CD (Section 2.1.2.2) is not expected to affect drug release from this formulation.

Administration of the multi-matrix formulation of mesalazine (Mezavant®, Lialda®, United States) in patients with UC could be affected by longer small intestinal and colonic transit times, as following the dissolution of the gastro-resistant coating drug release occurs after diffusion from the lipophilic and hydrophilic matrix (Section 2). Drug release might occur in more proximal GI compartments differing from controls in which disintegration of the formulation was observed between 4.8h and 17.4h after administration.[179]

Administration of a controlled release pellet formulation of budesonide (Entocort®, AstraZeneca UK Limited, UK) showed increased systemic bioavailability in CD patients

compared to controls (20.5 % (15.1, 27.8) vs. 11.5 % (8.8, 15.0), $AUC_{0-\infty}$ 114.0 nmol*h / L (81.4, 159.5) vs. 60.4 nmol*h / L (45.1, 80.8)).[40] This effect could be attributed to the delayed gastric emptying observed and other factors such as the composition of GI fluids, differences in permeability and the colonic bacterial and intestinal metabolism. Differences in the pharmacokinetics of budesonide in CD patients could possibly result in treatment failure or increased side effects.

4.2.2. pH-controlled release

The alteration of the typical pH profile in GI compartments changes the release profile of pharmaceutical formulations with pH sensitive coatings. For enteric coated formulations the reduction of acid in the stomach in CD can lead to premature drug release in the stomach (Section 2.1.2.2). Increased gastric residence time as observed in celiac disease, UC and CD could delay drug absorption of enteric coated formulations (Section 2).

Different mesalazine formulations with pH-controlled release behaviour are available for the therapy of IBD. Formulations with a coating of Eudragit-L (Salofalk®, Dr Falk GmbH, Freiburg, Germany), dissolving at pH ≥ 6, target the mid-ileum and colon, whereas a tablet coated with Eudragit S (Asacol®,Tillotts Pharma AG, Ziefen, Switzerland), dissolving at pH ≥ 7, targets the terminal ileum and colon.[179] Based on the lower colonic pH values in UC (Section 2.1.2.1), impairment of drug release from these formulations may take place where failure to reach the pH needed for dissolution of the polymer coating occurs.

4.3. Azo-bonded prodrug formulations

Colonic drug delivery, often used in IBD, can be achieved by administering prodrugs or polymer coatings, which are cleaved by colonic bacterial enzymes such as azoreductase leading subsequently to the release of the active metabolite/drug.

In GI diseases, three different aspects can affect drug release of azo-bonded prodrugs such as sulfasalazine and olsalazine. Firstly, a decreased intestinal transit time has been associated with less exposure of the prodrugs to bacterial action and enhanced faecal loss of the prodrugs.[180] The therapeutic efficacy could be affected in some IBD patients as colonic transit time was highly variable (Section 2.1.2). Secondly, reduced activity of bacterial azoreductase as observed in CD (Section 2.1.6.2) could lead to reduced prodrug activation. Thirdly, small intestinal bacterial overgrowth as observed in CD and UC (Section 2.1.6) could provoke prodrug activation in upper parts of the GI tract.

5. Methods to predict drug product performance

Throughout the different stages in pharmaceutical drug development, *in vitro* biorelevant release/dissolution models linked with physiologically based pharmacokinetic (PBPK) models are used to predict drug product performance.[12; 181] Media, that simulate closely the conditions in the GI tract of healthy subjects by incorporating e.g., phospholipids, bile salts and lipids, are termed biorelevant. By using biorelevant media and applying hydrodynamics to reflect the conditions in healthy subjects, successful predictions of the drug product performance can be established with *in vitro* dissolution/release testing.[182; 183] Nowadays, *in vitro* dissolution/release profiles are often further linked with PBPK models resulting in better *in vivo* predictions of drug bioavailability.[184-186] It should be noted that the design of *in vitro* dissolution/release and PBPK models is based on conditions in healthy subjects. A remaining challenge is the prediction of drug product performance in patients with GI diseases where absorption is expected to be impaired (Section 2). Therefore, the development of biorelevant *in vitro* dissolution/release tests in patients with GI diseases linked with PBPK models would be desirable. In the following sections, the need to develop both *in vitro* dissolution/release tests and PBPK models reflecting conditions found in GI disease which can be confidently used to predict drug product performance is discussed.

5.1. *In vitro* dissolution and release testing

In vitro dissolution testing has been established in the pharmaceutical industry for quality control purposes for stability testing and to assure batch to batch consistency. For drug development, biorelevant *in vitro* dissolution and release testing is used for the development of pharmaceutical formulations, to predict the *in vivo* performance of a drug product and to develop *in vitro/in vivo* correlations (IVIVC) with the intention to reduce time-consuming and cost-intensive animal or human studies. In the development of a suitable biorelevant *in vitro* dissolution testing method, the physicochemical characteristics of the drug and the physiological conditions in the GI tract should be considered. Current *in vitro* dissolution tests incorporate hydrodynamic conditions and media based on the physiological conditions in healthy subjects.

There is a need for biorelevant dissolution methodology to simulate the GI conditions in patients with GI diseases since pathophysiological changes (Section 2) are expected to have an impact on drug solubilisation and dissolution and subsequently on drug absorption. Currently, no *in vitro* dissolution and release tests reflect changes observed in patients with GI diseases.

In vitro dissolution and release tests used for drugs in GI diseases, especially IBD, have been developed reflecting mainly the GI pH profile in healthy subjects. To study the release and dissolution of different colon-targeting mesalazine and budesonide formulations several *in vitro* dissolution methods have been developed (Figure 5).[187-190] In terms of media, GI fluids were simulated using simple pharmacopeia buffers (SGF, SIF, SCoF), biorelevant media (Fasted state simulated intestinal fluid) or media enriched with enzymes. Different buffer systems were used (phosphate and bicarbonate) whereas bicarbonate buffers were superior in predicting the *in vivo* performance of mesalazine formulations.[191] The passage through the different GI compartments is simulated by media changes, modifications of the pH value at

various time points and the total duration of the experiment (360-1440min). The models vary in the applied hydrodynamics due to differences in volumes of the media (200ml-1000ml), in the agitation rate (50-100rpm, 10dips/min) and in the choice of the dissolution apparatus (USP II or III dissolution apparatus).

Bacterial enzymatic action, needed for colon-targeting drug delivery, was included in *in vitro* dissolution tests with USP dissolution apparatus in several ways spanning the simple addition of enzymes to the addition of rat caecal contents and human faecal slurries.[192] Drug metabolism by intestinal microbiota can further be tested in more complex *in vitro* GI simulators such as semi-continuous culture systems and continuous culture systems (e.g. TNO TIM-2 *in vitro* model of the colon) with anaerobic conditions in which pH, temperature and redox potential can be controlled.[11; 193; 194]

For the development of biorelevant *in vitro* dissolution and release tests for patients with GI diseases, pathophysiological changes in terms of media, hydrodynamics and microbiota must be reflected in the experimental design.

5.2. PBPK models

Physiologically based pharmacokinetic (PBPK) models use preclinical *in vitro* data, physicochemical drug properties and physiological parameters to predict *in vivo* plasma concentration-time profiles.[12] PBPK modelling was first introduced to assess the toxicology of drugs and was in recent years established as useful biopharmaceutical tool to predict drug bioavailability. The mathematical modelling framework used incorporates the different compartments of the GI tract and evaluates absorption, distribution, metabolism and elimination of the studied compound.

For patients with GI diseases PBPK models present a special opportunity to improve their drug therapy. Pathophysiological changes can affect drug absorption (Section 2) but only a minor part of drugs and pharmaceutical formulations is tested in a GI disease population. Especially for the medication of concomitant conditions, e.g. oncological or cardiovascular drugs, the impact of the GI disease on drug product performance is unknown. As human studies are very cost-intensive, this might not change in the coming years considering the heterogeneous and therefore small patient population in the different types of GI disease. Establishing predictive *in silico* models for the different GI disease states can help to implement appropriate dosing regimen and improve drug therapy management.

For GI diseases, PBPK models should include all the pathophysiological changes relevant for drug absorption in patients with GI diseases compared to healthy subjects (Section 2). However, due to only a limited number of studies with small patient populations and a high inter- and intra-study variability the characterisation of the pathophysiological changes is challenging. Up to now, no PBPK models for patients with GI diseases have been developed but recently a PBPK model for patients after bariatric surgery (post sleeve gastrectomy, post Roux-en-Y gastric bypass, post biliopancreatic diversion with duodenal switch, post jejunoileal

836 bypass) was developed.[195] The virtual model showed that the bioavailability of 5 drugs
837 (omeprazole, diclofenac, fluconazole, ciprofloxacin, simvastatin) in patients after bariatric
838 surgery was highly dependent on drug-specific parameters. The model, based on the template
839 for morbidly obese in the Simcyp Simulator v10 (Simcyp Limited, Sheffield, UK), integrated
840 changes in gastric volume and emptying rate, GI pH, differences in small intestinal dimensions
841 and motility, transit time, bile properties, renal function and serum protein levels as observed
842 in literature. Predictions of oral bioavailability of atorvastatin and cyclosporine in patients post
843 Roux-en-Y gastric bypass were confirmed by clinical data, however the absorption of
844 atorvastatin was not captured in the model for patients with post biliopancreatic diversion with
845 duodenal switch.[196]

846 **6. Conclusion and outlook**

847 Further elucidation of drug absorption profiles in patients with GI diseases could be highly
848 beneficial. The significance of current studies is often limited by small patient populations,
849 conflicting data and the difficulty to assess changes in different disease states. More *in vivo*
850 data is needed to further assess the GI physiological conditions in patients with GI diseases.
851 Oral absorption already shows a high interindividual variability in healthy adults. Different
852 disease states and disease localization make it even more difficult to assess absorption profiles
853 in this heterogeneous group. In order to improve drug therapy for patients with GI diseases
854 their medication should be tested under conditions specific to the particular pathophysiology.
855 The ability to predict the *in vivo* performance of drug products in patients with GI diseases will
856 be contingent on the development of appropriate biorelevant dissolution testing linked with
857 PBPK models simulating pathophysiological conditions. Medication for concomitant diseases
858 is seldom tested in GI disease patients. For these drugs the development of more cost-effective
859 and less time-consuming alternatives to expensive clinical trials would represent an opportunity
860 to improve drug therapy. Predicting the probability that a drug will be affected by certain GI

diseases depending on its physicochemical properties, would further limit the amount of experimental and computational work required.

7. Acknowledgements

This work is part of a project that has received funding from Horizon 2020 Marie Sklodowska-Curie Innovative Training Networks programme under grant agreement No. 674909.

References

1. Fleisher D *et al*. Drug, Meal and Formulation Interactions Influencing Drug Absorption after Oral Administration. Clinical Implications. *Clin Pharmacokinet* 1999; 3: 233-54.
2. Karalis V *et al*. Bioavailability and Bioequivalence: Focus on Physiological Factors and Variability. *Pharm Res* 2008; 8: 1956-62.
3. Hamedani R *et al*. Review Article: Drug Development in Inflammatory Bowel Disease: Budesonide--a Model of Targeted Therapy. *Aliment Pharmacol Ther* 1997: 98-107; discussion 107-8.
4. Tran TH *et al*. Drug Absorption in Celiac Disease. *Am J Health Syst Pharm* 2013; 24: 2199-206.
5. Faye E *et al*. Antidepressant Agents in Short Bowel Syndrome. *Clin Ther* 2014; 12: 2029-2033 e3.
6. Malayandi R *et al*. Biopharmaceutical Considerations and Characterizations in Development of Colon Targeted Dosage Forms for Inflammatory Bowel Disease. *Drug Deliv Transl Res* 2014; 2: 187-202.
7. Bassotti G *et al*. Colonic Motility in Ulcerative Colitis. *United European Gastroenterol J* 2014; 6: 457-62.
8. Bai JPF *et al*. Literature Review of Gastrointestinal Physiology in the Elderly, in Pediatric Patients, and in Patients with Gastrointestinal Diseases. *J Pharm Sci* 2016; 2: 476-483.
9. Arrieta MC *et al*. Alterations in Intestinal Permeability. *Gut* 2006; 10: 1512-20.
10. Enright EF *et al*. The Impact of the Gut Microbiota on Drug Metabolism and Clinical Outcome. *Yale J Biol Med* 2016; 3: 375-382.
11. Sousa T *et al*. The Gastrointestinal Microbiota as a Site for the Biotransformation of Drugs. *Int J Pharm* 2008; 1-2: 1-25.
12. Kostewicz ES *et al*. Pbpk Models for the Prediction of in Vivo Performance of Oral Dosage Forms. *Eur J Pharm Sci* 2014: 300-21.
13. Dressman JB *et al*. Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms. *Pharm Res* 1998; 1: 11-22.
14. Stefanelli T *et al*. New Insights into Inflammatory Bowel Disease Pathophysiology: Paving the Way for Novel Therapeutic Targets. *Curr Drug Targets* 2008; 5: 413-8.
15. Hanauer SB. Inflammatory Bowel Disease: Epidemiology, Pathogenesis, and Therapeutic Opportunities. *Inflamm Bowel Dis* 2006: S3-9.
16. Kaplan GG. The Global Burden of Ibd: From 2015 to 2025. *Nat Rev Gastroenterol Hepatol* 2015; 12: 720-727.
17. Vladan M, Jürgen S. Gastrointestinal Disease and Dosage Form Performance. *Oral Drug Absorption.* CRC Press, 2010: 127-137.
18. Satsangi J *et al*. The Montreal Classification of Inflammatory Bowel Disease: Controversies, Consensus, and Implications. *Gut* 2006; 6: 749-753.

19. Deroche TC *et al*. Histological Evaluation in Ulcerative Colitis. *Gastroenterol Rep (Oxf)* 2014; 3: 178-92.
20. Da Silva BC *et al*. Epidemiology, Demographic Characteristics and Prognostic Predictors of Ulcerative Colitis. *World J Gastroenterol* 2014; 28: 9458-67.
21. Abraham C, Cho JH. Inflammatory Bowel Disease. *N Engl J Med* 2009; 21: 2066-78.
22. Furukawa A *et al*. Cross-Sectional Imaging in Crohn Disease. *Radiographics* 2004; 3: 689-702.
23. Haase AM *et al*. Regional Gastrointestinal Transit Times in Severe Ulcerative Colitis. *Neurogastroenterol Motil* 2016; 2: 217-24.
24. Rao SS, Read NW. Gastrointestinal Motility in Patients with Ulcerative Colitis. *Scandinavian journal of gastroenterology Supplement* 1990: 22-8.
25. Ewe K *et al*. Inflammation Does Not Decrease Intraluminal Ph in Chronic Inflammatory Bowel Disease. *Dig Dis Sci* 1999; 7: 1434-1439.
26. Fallingborg J *et al*. Very Low Intraluminal Colonic Ph in Patients with Active Ulcerative Colitis. *Dig Dis Sci* 1993; 11: 1989-1993.
27. Bosworth BP *et al*. W1229 Colonic Ph Is Lower in Patients with Mild Ulcerative Colitis Compared to Normal Controls. *Gastroenterology* 2009; 5: A-682-A-683.
28. Nugent SG *et al*. Gut Ph and Transit Time in Ulcerative Colitis Appear Sufficient for Complete Dissolution of Ph-Dependent 5-Asa-Containing Capsules. *Gastroenterology* 2000; 4: A781.
29. Rana SV *et al*. Small Intestinal Bacterial Overgrowth and Orocecal Transit Time in Patients of Inflammatory Bowel Disease. *Dig Dis Sci* 2013; 9: 2594-8.
30. Fischer M *et al.* Assessment of Small Intestinal Transit Times in Ulcerative Colitis and Crohn's Disease Patients with Different Disease Activity Using Video Capsule Endoscopy. *AAPS PharmSciTech* 2017; 2: 404-409.
31. Hardy J *et al*. Gastrointestinal Transit of Small Tablets in Patients with Ulcerative Colitis. *International Journal of Pharmaceutics* 1988; 1-3: 79-82.
32. Davis SS *et al*. Transit of Pharmaceutical Dosage Forms through the Small Intestine. *Gut* 1986; 8: 886-892.
33. Hardy JG *et al*. Evaluation of an Enteric-Coated Delayed-Release 5-Aminosalicylic Acid Tablet in Patients with Inflammatory Bowel Disease. *Aliment Pharmacol Ther* 1987; 4: 273-80.
34. Akerman A *et al*. Computational Postprocessing Quantification of Small Bowel Motility Using Magnetic Resonance Images in Clinical Practice: An Initial Experience. *J Magn Reson Imaging* 2016; 2: 277-87.
35. Bassotti G *et al*. Colonic Propulsive and Postprandial Motor Activity in Patients with Ulcerative Colitis in Remission. *Eur J Gastroenterol Hepatol* 2006; 5: 507-10.
36. Press AG *et al*. Gastrointestinal Ph Profiles in Patients with Inflammatory Bowel Disease. *Aliment Pharmacol Ther* 1998; 7: 673-8.

938 37. Vertzoni M *et al*. Characterization of the Ascending Colon Fluids in Ulcerative Colitis. *Pharm*
939 *Res* 2010; 8: 1620-6.
940 38. Raimundo A *et al*. Gastrointestinal Ph Profiles in Ulcerative Colitis. *Gastroenterology* 1992; 4:
941 A681.
942 39. Diakidou A *et al*. Characterization of the Contents of Ascending Colon to Which Drugs Are
943 Exposed after Oral Administration to Healthy Adults. *Pharm Res* 2009; 9: 2141-51.
944 40. Edsbacker S *et al*. A Pharmacoscintigraphic Evaluation of Oral Budesonide Given as Controlled-
945 Release (Entocort) Capsules. *Aliment Pharmacol Ther* 2003; 4: 525-36.
946 41. Niv E *et al*. Sequential Capsule Endoscopy of the Small Bowel for Follow-up of Patients with
947 Known Crohn's Disease. *J Crohns Colitis* 2014; 12: 1616-23.
948 42. Tursi A *et al*. Assessment of Orocaecal Transit Time in Different Localization of Crohn's Disease
949 and Its Possible Influence on Clinical Response to Therapy. *Eur J Gastroenterol Hepatol*
950 2003; 1: 69-74.
951 43. Sasaki Y *et al*. Improved Localizing Method of Radiopill in Measurement of Entire
952 Gastrointestinal Ph Profiles: Colonic Luminal Ph in Normal Subjects and Patients with
953 Crohn's Disease. *Am J Gastroenterol* 1997; 1: 114-8.
954 44. Fallingborg J *et al*. Small Intestinal Transit Time and Intraluminal Ph in Ileocecal Resected
955 Patients with Crohn's Disease. *Dig Dis Sci* 1998; 4: 702-5.
956 45. Winter TA *et al*. Impaired Gastric Acid and Pancreatic Enzyme Secretion in Patients with Crohn's
957 Disease May Be a Consequenece of a Poor Nutritional State. *Inflamm Bowel Dis* 2004; 5:
958 618-25.
959 46. Nobrega AC *et al*. Dyspeptic Symptoms and Delayed Gastric Emptying of Solids in Patients with
960 Inactive Crohn's Disease. *BMC Gastroenterol* 2012: 175.
961 47. Karner M *et al*. First Multicenter Study of Modified Release Phosphatidylcholine "Lt-02" in
962 Ulcerative Colitis: A Randomized, Placebo-Controlled Trial in Mesalazine-Refractory
963 Courses. *Am J Gastroenterol* 2014; 7: 1041-51.
964 48. Ehehalt R *et al*. Phosphatidylcholine and Lysophosphatidylcholine in Intestinal Mucus of
965 Ulcerative Colitis Patients. A Quantitative Approach by Nanoelectrospray-Tandem Mass
966 Spectrometry. *Scand J Gastroenterol* 2004; 8: 737-42.
967 49. Braun A *et al*. Alterations of Phospholipid Concentration and Species Composition of the
968 Intestinal Mucus Barrier in Ulcerative Colitis: A Clue to Pathogenesis. *Inflamm Bowel Dis*
969 2009; 11: 1705-20.
970 50. Schilli R *et al*. Comparison of the Composition of Faecal Fluid in Crohn's Disease and Ulcerative
971 Colitis. *Gut* 1982; 4: 326-332.
972 51. Nishida T *et al*. Bile Acid Absorption Kinetics in Crohn's Disease on Elemental Diet after Oral
973 Administration of a Stable-Isotope Tracer with Chenodeoxycholic-11, 12-D2 Acid. *Gut* 1982;
974 9: 751-7.

975 52. Rutgeerts P *et al*. Bile Acid Studies in Patients with Crohn's Colitis. *Gut* 1979; 12: 1072-1077.
976 53. Vantrappen G *et al*. Bile Acid Studies in Uncomplicated Crohn's Disease. *Gut* 1977; 9: 730-735.
977 54. Barkun AN *et al*. Bile Acid Malabsorption in Chronic Diarrhea: Pathophysiology and Treatment.
978 *Can J Gastroenterol* 2013; 11: 653-9.
979 55. Lenz K *et al*. Bile Acid Metabolism and Plasma Protein Turnover in Crohn's Disease. *Scand J*
980 *Gastroenterol* 1976; 7: 721-7.
981 56. Lenicek M *et al*. Bile Acid Malabsorption in Inflammatory Bowel Disease: Assessment by Serum
982 Markers. *Inflamm Bowel Dis* 2011; 6: 1322-7.
983 57. Vernia P *et al*. Organic Anions and the Diarrhea of Inflammatory Bowel Disease. *Dig Dis Sci*
984 1988; 11: 1353-8.
985 58. Hegnhøj J *et al*. Pancreatic Function in Crohn's Disease. *Gut* 1990; 9: 1076-1079.
986 59. Angelini G *et al*. Pancreatic Function in Chronic Inflammatory Bowel Disease. *Int J Pancreatol*
987 1988; 2-3: 185-93.
988 60. Russel FGM. Transporters: Importance in Drug Absorption, Distribution, and Removal. In: Pang,
989 K. S., et al eds. *Enzyme- and Transporter-Based Drug-Drug Interactions: Progress and*
990 *Future Challenges*. New York, NY: Springer New York, 2010: 27-49.
991 61. Estudante M *et al*. Intestinal Drug Transporters: An Overview. *Advanced Drug Delivery Reviews*
992 2013; 10: 1340-1356.
993 62. Pullan RD *et al*. Thickness of Adherent Mucus Gel on Colonic Mucosa in Humans and Its
994 Relevance to Colitis. *Gut* 1994; 3: 353-9.
995 63. The International Transporter Consortium. Membrane Transporters in Drug Development. *Nature*
996 *Reviews Drug Discovery* 2010; 3: 215-236.
997 64. Englund G *et al*. Efflux Transporters in Ulcerative Colitis: Decreased Expression of Bcrp (Abcg2)
998 and Pgp (Abcb1). *Inflamm Bowel Dis* 2007; 3: 291-7.
999 65. Plewka D *et al*. Expression of Selected Cytochrome P450 Isoforms and of Cooperating Enzymes
1000 in Colorectal Tissues in Selected Pathological Conditions. *Pathol Res Pract* 2014; 4: 242-9.
1001 66. Söderholm JD *et al*. Augmented Increase in Tight Junction Permeability by Luminal Stimuli in the
1002 Non-Inflamed Ileum of Crohn's Disease. *Gut* 2002; 3: 307-313.
1003 67. Jenkins RT *et al*. Small Bowel and Colonic Permeability to 51cr-Edta in Patients with Active
1004 Inflammatory Bowel Disease. *Clin Invest Med* 1988; 2: 151-5.
1005 68. Resnick RH *et al*. Intestinal Permeability in Gastrointestinal Disorders. Use of Oral [99mtc]Dtpa.
1006 *Dig Dis Sci* 1990; 2: 205-11.
1007 69. Pironi L *et al*. Relationship between Intestinal Permeability to [51cr]Edta and Inflammatory
1008 Activity in Asymptomatic Patients with Crohn's Disease. *Dig Dis Sci* 1990; 5: 582-8.
1009 70. Wyatt J *et al*. Increased Gastric and Intestinal Permeability in Patients with Crohn's Disease. *Am J*
1010 *Gastroenterol* 1997; 10: 1891-6.
1011 71. Johnston SD *et al*. Intestinal Permeability Tests in Coeliac Disease. *Clin Lab* 2001; 3-4: 143-50.

72. Benjamin J *et al*. Intestinal Permeability and Its Association with the Patient and Disease Characteristics in Crohn's Disease. *World J Gastroenterol* 2008; 9: 1399-405.
73. Menard S *et al*. Multiple Facets of Intestinal Permeability and Epithelial Handling of Dietary Antigens. *Mucosal Immunol* 2010; 3: 247-59.
74. Buchman AL *et al*. A Higher Dose Requirement of Tacrolimus in Active Crohn's Disease May Be Related to a High Intestinal P-Glycoprotein Content. *Dig Dis Sci* 2005; 12: 2312-2315.
75. Klotz U *et al*. Expression of Intestinal Drug-Metabolizing Enzymes in Patients with Chronic Inflammatory Bowel Disease. *Current Therapeutic Research* 1998; 8: 556-563.
76. Ramakrishna BS *et al*. Impaired Sulphation of Phenol by the Colonic Mucosa in Quiescent and Active Ulcerative Colitis. *Gut* 1991; 1: 46-9.
77. Haderslev KV *et al*. Paracetamol Metabolism in Patients with Ulcerative Colitis. *British Journal of Clinical Pharmacology* 1998; 5: 513-516.
78. Fakhoury M *et al*. Impact of Inflammation on the Duodenal Mrna Expression of Cyp3a and P-Glycoprotein in Children with Crohn's Disease. *Inflamm Bowel Dis* 2006; 8: 745-9.
79. Wilson A *et al*. Cyp3a4 Activity Is Markedly Lower in Patients with Crohn's Disease. *Inflamm Bowel Dis* 2017; 5: 804-813.
80. Sartor RB, Wu GD. Roles for Intestinal Bacteria, Viruses, and Fungi in Pathogenesis of Inflammatory Bowel Diseases and Therapeutic Approaches. *Gastroenterology* 2017; 2: 327-339.e4.
81. Qin J *et al*. A Human Gut Microbial Gene Catalogue Established by Metagenomic Sequencing. *Nature* 2010; 7285: 59-65.
82. Forbes JD *et al*. The Gut Microbiota in Immune-Mediated Inflammatory Diseases. *Front Microbiol* 2016: 1081.
83. Morgan XC *et al*. Dysfunction of the Intestinal Microbiome in Inflammatory Bowel Disease and Treatment. *Genome Biol* 2012; 9: R79.
84. Machiels K *et al*. A Decrease of the Butyrate-Producing Species Roseburia Hominis and Faecalibacterium Prausnitzii Defines Dysbiosis in Patients with Ulcerative Colitis. *Gut* 2014; 8: 1275-83.
85. Carrette O *et al*. Bacterial Enzymes Used for Colon-Specific Drug Delivery Are Decreased in Active Crohn's Disease. *Dig Dis Sci* 1995; 12: 2641-2646.
86. Rafii F *et al*. Azoreductase Activity of Anaerobic Bacteria Isolated from Human Intestinal Microflora. *Appl Environ Microbiol* 1990; 7: 2146-51.
87. Thibault R *et al*. Butyrate Utilization by the Colonic Mucosa in Inflammatory Bowel Diseases: A Transport Deficiency. *Inflamm Bowel Dis* 2010; 4: 684-95.
88. Wang ZK *et al*. Intestinal Microbiota Pathogenesis and Fecal Microbiota Transplantation for Inflammatory Bowel Disease. *World J Gastroenterol* 2014; 40: 14805-20.

89. Ohkusa T, Koido S. Intestinal Microbiota and Ulcerative Colitis. *J Infect Chemother* 2015; 11: 761-8.
90. Corfield AP *et al*. Degradation by Bacterial Enzymes of Colonic Mucus from Normal Subjects and Patients with Inflammatory Bowel Disease: The Role of Sialic Acid Metabolism and the Detection of a Novel O-Acetylsialic Acid Esterase. *Clin Sci (Lond)* 1988; 1: 71-8.
91. Wright EK *et al*. Recent Advances in Characterizing the Gastrointestinal Microbiome in Crohn's Disease: A Systematic Review. *Inflamm Bowel Dis* 2015; 6: 1219-28.
92. Perri F *et al*. Gastric Emptying of Solids Is Delayed in Celiac Disease and Normalizes after Gluten Withdrawal. *Acta Paediatr* 2000; 8: 921-5.
93. Green PH, Jabri B. Celiac Disease. *Annu Rev Med* 2006: 207-21.
94. Ciaccio EJ *et al*. Recommendations to Quantify Villous Atrophy in Video Capsule Endoscopy Images of Celiac Disease Patients. *World J Gastrointest Endosc* 2016; 18: 653-662.
95. Battaglia E *et al*. Gluten-Free Diet Normalizes Mouth-to-Cecum Transit of a Caloric Meal in Adult Patients with Celiac Disease. *Dig Dis Sci* 1997; 10: 2100-2105.
96. Spiller RC *et al*. Delayed Postprandial Plasma Bile Acid Response in Coeliac Patients with Slow Mouth-Caecum Transit. *Clin Sci (Lond)* 1987; 2: 217-23.
97. Bai JC *et al*. Abnormal Colonic Transit Time in Untreated Celiac Sprue. *Acta Gastroenterol Latinoam* 1995; 5: 277-84.
98. Benini L *et al*. Gastric Emptying of Realistic Meals with and without Gluten in Patients with Coeliac Disease. Effect of Jejunal Mucosal Recovery. *Scand J Gastroenterol* 2001; 10: 1044-8.
99. Bardella MT *et al*. Gastric Emptying and Plasma Neurotensin Levels in Untreated Celiac Patients. *Scand J Gastroenterol* 2000; 3: 269-73.
100. Urgesi R *et al*. Evaluation of Gastric and Small Bowel Transit Times in Coeliac Disease with the Small Bowel Pillcam(R): A Single Centre Study in a Non Gluten-Free Diet Adult Italian Population with Coeliac Disease. *Eur Rev Med Pharmacol Sci* 2013; 9: 1167-73.
101. Usai P *et al*. Oesophageal Motility in Adult Coeliac Disease. *Neurogastroenterol Motil* 1995; 4: 239-44.
102. Kitis G *et al*. Altered Jejunal Surface Ph in Coeliac Disease: Its Effect on Propranolol and Folic Acid Absorption. *Clin Sci (Lond)* 1982; 4: 373-80.
103. Lucas ML *et al*. Acid Microclimate in Coeliac and Crohn's Disease: A Model for Folate Malabsorption. *Gut* 1978; 8: 735-42.
104. Benn A, Cooke WT. Intraluminal Ph of Duodenum and Jejunum in Fasting Subjects with Normal and Abnormal Gastric or Pancreatic Function. *Scand J Gastroenterol* 1971; 4: 313-7.
105. Carroccio A *et al*. Exocrine Pancreatic Function in Children with Coeliac Disease before and after a Gluten Free Diet. *Gut* 1991; 7: 796-9.

106. Lanzini A, Lanzarotto F. Review Article: The 'Mechanical Pumps' and the Enterohepatic Circulation of Bile Acids--Defects in Coeliac Disease. *Aliment Pharmacol Ther* 2000: 58-61.
107. Low-Beer TS *et al*. Gallbladder Inertia and Sluggish Enterohepatic Circulation of Bile-Salts in Cœliac Disease. *The Lancet* 1971; 7707: 991-994.
108. Vuoristo M, Miettinen TA. Increased Biliary Lipid Secretion in Celiac Disease. *Gastroenterology* 1985; 1: 134-142.
109. Lavo B *et al*. Signs of Increased Leakage over the Jejunal Mucosa During Gliadin Challenge of Patients with Coeliac Disease. *Gut* 1990; 2: 153-7.
110. Kuitunen M, Savilahti E. Gut Permeability to Human Alpha-Lactalbumin, Beta-Lactoglobulin, Mannitol, and Lactulose in Celiac Disease. *J Pediatr Gastroenterol Nutr* 1996; 2: 197-204.
111. Ukabam SO, Cooper BT. Small Intestinal Permeability to Mannitol, Lactulose, and Polyethylene Glycol 400 in Celiac Disease. *Dig Dis Sci* 1984; 9: 809-16.
112. Vilela EG *et al*. Gut Permeability to Lactulose and Mannitol Differs in Treated Crohn's Disease and Celiac Disease Patients and Healthy Subjects. *Braz J Med Biol Res* 2008; 12: 1105-9.
113. Bjarnason I *et al*. Comparison of Four Markers of Intestinal Permeability in Control Subjects and Patients with Coeliac Disease. *Scand J Gastroenterol* 1994; 7: 630-9.
114. Vannay A *et al*. Increased Expression of Hypoxia-Inducible Factor 1[Agr] in Coeliac Disease. *Pediatr Res* 2010; 2: 118-122.
115. Lang CC *et al*. Decreased Intestinal Cyp3a in Celiac Disease: Reversal after Successful Gluten-Free Diet: A Potential Source of Interindividual Variability in First-Pass Drug Metabolism. *Clin Pharmacol Ther* 1996; 1: 41-6.
116. Johnson TN *et al*. Enterocytic Cyp3a4 in a Paediatric Population: Developmental Changes and the Effect of Coeliac Disease and Cystic Fibrosis. *Br J Clin Pharmacol* 2001; 5: 451-60.
117. Marasco G *et al*. Gut Microbiota and Celiac Disease. *Dig Dis Sci* 2016; 6: 1461-72.
118. Mooney PD *et al*. Letter: Coeliac Disease and Small Intestinal Bacterial Overgrowth--Is Dysmotility the Missing Link? *Aliment Pharmacol Ther* 2014; 8: 902-3.
119. Lasa JS *et al*. Small Intestinal Bacterial Overgrowth Prevalence in Celiac Disease Patients Is Similar in Healthy Subjects and Lower in Irritable Bowel Syndrome Patients. *Rev Gastroenterol Mex* 2015; 2: 171-4.
120. Zwolinska-Wcislo M *et al*. Small Intestinal Bacterial Overgrowth and Gastrointestinal Symptoms in Celiac Disease Patients and in Patients Receiving Proton Pomp Inhibitors. *United European Gastroenterology Journal* 2013; 1: A579.
121. Losurdo G *et al*. Small Intestinal Bacterial Overgrowth and Celiac Disease: A Systematic Review with Pooled-Data Analysis. *Neurogastroenterol Motil* 2017; 6.
122. Spiller R *et al*. Guidelines on the Irritable Bowel Syndrome: Mechanisms and Practical Management. *Gut* 2007; 12: 1770-98.

123. Lalezari D. Gastrointestinal Ph Profile in Subjects with Irritable Bowel Syndrome. *Ann Gastroenterol* 2012; 4: 333-337.
124. Cann PA *et al*. Irritable Bowel Syndrome: Relationship of Disorders in the Transit of a Single Solid Meal to Symptom Patterns. *Gut* 1983; 5: 405-11.
125. Wedlake L *et al*. Systematic Review: The Prevalence of Idiopathic Bile Acid Malabsorption as Diagnosed by Sehcat Scanning in Patients with Diarrhoea-Predominant Irritable Bowel Syndrome. *Aliment Pharmacol Ther* 2009; 7: 707-17.
126. Dior M *et al*. Interplay between Bile Acid Metabolism and Microbiota in Irritable Bowel Syndrome. *Neurogastroenterol Motil* 2016; 9: 1330-40.
127. Camilleri M, Gorman H. Intestinal Permeability and Irritable Bowel Syndrome. *Neurogastroenterol Motil* 2007; 7: 545-52.
128. Lee JW *et al*. Subjects with Diarrhea-Predominant Ibs Have Increased Rectal Permeability Responsive to Tryptase. *Dig Dis Sci* 2010; 10: 2922-8.
129. Parkes GC *et al*. Distinct Microbial Populations Exist in the Mucosa-Associated Microbiota of Sub-Groups of Irritable Bowel Syndrome. *Neurogastroenterol Motil* 2012; 1: 31-9.
130. Jeffery IB *et al*. An Irritable Bowel Syndrome Subtype Defined by Species-Specific Alterations in Faecal Microbiota. *Gut* 2012; 7: 997-1006.
131. Rajilic-Stojanovic M *et al*. Global and Deep Molecular Analysis of Microbiota Signatures in Fecal Samples from Patients with Irritable Bowel Syndrome. *Gastroenterology* 2011; 5: 1792-801.
132. Malinen E *et al*. Analysis of the Fecal Microbiota of Irritable Bowel Syndrome Patients and Healthy Controls with Real-Time Pcr. *Am J Gastroenterol* 2005; 2: 373-82.
133. Carroll RE *et al*. Management and Complications of Short Bowel Syndrome: An Updated Review. *Curr Gastroenterol Rep* 2016; 7: 40.
134. Boccia S *et al*. Intestinal Microbiota in Adult Patients with Short Bowel Syndrome: Preliminary Results from a Pilot Study. *Clin Nutr* 2016.
135. Severijnen R *et al*. Enteral Drug Absorption in Patients with Short Small Bowel : A Review. *Clin Pharmacokinet* 2004; 14: 951-62.
136. O'keefe SJ *et al*. Short Bowel Syndrome and Intestinal Failure: Consensus Definitions and Overview. *Clin Gastroenterol Hepatol* 2006; 1: 6-10.
137. Broadbent AM *et al*. A Review of Short Bowel Syndrome and Palliation: A Case Report and Medication Guideline. *J Palliat Med* 2006; 6: 1481-91.
138. Compher C *et al*. Noninvasive Measurement of Transit Time in Short Bowel Syndrome. *JPEN J Parenter Enteral Nutr* 2007; 3: 240-5.
139. Mansbach CM, 2nd *et al*. Fat Digestion in Patients with Bile Acid Malabsorption but Minimal Steatorrhea. *Dig Dis Sci* 1980; 5: 353-62.

140. Fitzpatrick WJ *et al*. Ileal Resection: Effect of Cimetidine and Taurine on Intrajejunal Bile Acid Precipitation and Lipid Solubilisation. *Gut* 1986; 1: 66-72.
141. Van Deest BW *et al*. Bile Salt and Micellar Fat Concentration in Proximal Small Bowel Contents of Ileectomy Patients. *J Clin Invest* 1968; 6: 1314-24.
142. Kumpf VJ. Pharmacologic Management of Diarrhea in Patients with Short Bowel Syndrome. *JPEN J Parenter Enteral Nutr* 2014; 1 Suppl: 38S-44S.
143. Pironi L. Definitions of Intestinal Failure and the Short Bowel Syndrome. *Best Pract Res Clin Gastroenterol* 2016; 2: 173-85.
144. Hofmann AF, Poley JR. Role of Bile Acid Malabsorption in Pathogenesis of Diarrhea and Steatorrhea in Patients with Ileal Resection. *Gastroenterology* 1972; 5: 918-934.
145. Tappenden KA. Pathophysiology of Short Bowel Syndrome: Considerations of Resected and Residual Anatomy. *JPEN J Parenter Enteral Nutr* 2014; 1 Suppl: 14s-22s.
146. Tappenden KA. Intestinal Adaptation Following Resection. *JPEN J Parenter Enteral Nutr* 2014; 1 Suppl: 23s-31s.
147. Ziegler TR *et al*. Distribution of the H+/Peptide Transporter Pept1 in Human Intestine: Up-Regulated Expression in the Colonic Mucosa of Patients with Short-Bowel Syndrome. *Am J Clin Nutr* 2002; 5: 922-30.
148. Joly F *et al*. Morphological Adaptation with Preserved Proliferation/Transporter Content in the Colon of Patients with Short Bowel Syndrome. *Am J Physiol Gastrointest Liver Physiol* 2009; 1: G116-23.
149. Joly F *et al*. Morphological Adaptation with Preserved Proliferation/Transporter Content in the Colon of Patients with Short Bowel Syndrome. *American Journal of Physiology - Gastrointestinal and Liver Physiology* 2009; 1: G116-G123.
150. Helen Chan O, Stewart BH. Physicochemical and Drug-Delivery Considerations for Oral Drug Bioavailability. *Drug Discovery Today* 1996; 11: 461-473.
151. Avdeef A. Physicochemical Profiling (Solubility, Permeability and Charge State). *Curr Top Med Chem* 2001; 4: 277-351.
152. Parsons RL *et al*. The Absorption of Antibiotics in Adult Patients with Coeliac Disease. *J Antimicrob Chemother* 1975; 1: 39-50.
153. World Health Organization. Proposal to Waive in Vivo Bioequivalence Requirements for Who Model List of Essential Medicines Immediate-Release, Solid Oral Dosage Forms. *WHO Technical Report Series* 2006: 391-438.
154. Renwick AG *et al*. The Absorption and Conjugation of Methyldopa in Patients with Coeliac and Crohn's Diseases During Treatment. *Br J Clin Pharmacol* 1983; 1: 77-83.
155. Nyholm D *et al*. Pharmacokinetics of Levodopa, Carbidopa, and 3-O-Methyldopa Following 16-Hour Jejunal Infusion of Levodopa-Carbidopa Intestinal Gel in Advanced Parkinson's Disease Patients. *AAPS J* 2013; 2: 316-23.

156. Lu HH *et al*. Influence of D-Glucose-Induced Water Absorption on Rat Jejunal Uptake of Two Passively Absorbed Drugs. *J Pharm Sci* 1992; 1: 21-5.
157. Holt S *et al*. Acetaminophen Absorption and Metabolism in Celiac Disease and Crohn's Disease. *Clin Pharmacol Ther* 1981; 2: 232-8.
158. Ueno T *et al*. Serum Drug Concentrations after Oral Administration of Paracetamol to Patients with Surgical Resection of the Gastrointestinal Tract. *Br J Clin Pharmacol* 1995; 3: 330-2.
159. Hansch C *et al*. *Exploring Qsar: Hydrophobic, Electronic, and Steric Constants*: American Chemical Society, Washington, DC, 1995.
160. Deibert P *et al*. High Variation of Tioguanine Absorption in Patients with Chronic Active Crohn's Disease. *Aliment Pharmacol Ther* 2003; 2: 183-9.
161. Varma MV *et al*. Physicochemical Space for Optimum Oral Bioavailability: Contribution of Human Intestinal Absorption and First-Pass Elimination. *J Med Chem* 2010; 3: 1098-108.
162. Chen M *et al*. High Lipophilicity and High Daily Dose of Oral Medications Are Associated with Significant Risk for Drug-Induced Liver Injury. *Hepatology* 2013; 1: 388-396.
163. Schneider RE *et al*. Plasma Levels of Propranolol in Treated Patients with Coeliac Disease and Patients with Crohn's Disease. *Br Med J* 1976; 6039: 794-5.
164. Avdeef A. Ph-Metric Log P. Ii: Refinement of Partition Coefficients and Ionization Constants of Multiprotic Substances. *J Pharm Sci* 1993; 2: 183-90.
165. Parsons RL *et al*. Absorption of Propranolol and Practolol in Coeliac Disease. *Gut* 1976; 2: 139-43.
166. Sandle GI *et al*. Propranolol Absorption in Untreated Coeliac Disease. *Clin Sci (Lond)* 1982; 1: 81-5.
167. Collins D *et al*. Celiac Disease and Hypothyroidism. *Am J Med* 2012; 3: 278-82.
168. Kasim NA *et al*. Molecular Properties of Who Essential Drugs and Provisional Biopharmaceutical Classification. *Mol Pharm* 2004; 1: 85-96.
169. Rodrigues CA *et al.* Prednisolone Absorption in Inflammatory Bowel Disease: Correlation with Anatomical Site and Extent. *Aliment Pharmacol Ther* 1987; 5: 391-9.
170. Shaffer JA *et al*. Absorption of Prednisolone in Patients with Crohn's Disease. *Gut* 1983; 3: 182-6.
171. Tanner AR *et al.* Serum Prednisolone Levels in Crohn's Disease and Coeliac Disease Following Oral Prednisolone Administration. *Digestion* 1981; 6: 310-5.
172. Pickup ME *et al*. Prednisolone Absorption in Coeliac Disease. *Eur J Drug Metab Pharmacokinet* 1979; 2: 87-9.
173. Kataoka M *et al*. Effects of Gastric Ph on Oral Drug Absorption: In Vitro Assessment Using a Dissolution/Permeation System Reflecting the Gastric Dissolution Process. *Eur J Pharm Biopharm* 2016: 103-11.

174. Ungell A-LB. Drug Transport Mechanisms across the Intestinal Epithelium. *Oral Drug Absorption*. CRC Press, 2010: 21-40.
175. Moffat AC *et al*. *Clarke's Analysis of Drugs & Poisons: In Pharmaceuticals, Body Fluids and Postmortem Material*: Pharmaceutical Press, 2003.
176. Milman N. Intestinal Absorption of Folic Acid - New Physiologic & Molecular Aspects. *Indian J Med Res* 2012; 5: 725-8.
177. Parsons RL *et al*. Pharmacokinetics of Salicylate and Indomethacin in Coeliac Disease. *Eur J Clin Pharmacol* 1977; 6: 473-7.
178. Faye E *et al*. Absorption and Efficacy of Acetylsalicylic Acid in Patients with Short Bowel Syndrome. *Ann Pharmacother* 2014; 6: 705-10.
179. Ye B, Van Langenberg DR. Mesalazine Preparations for the Treatment of Ulcerative Colitis: Are All Created Equal? *World J Gastrointest Pharmacol Ther* 2015; 4: 137-44.
180. Christensen LA *et al*. Release of 5-Aminosalicylic Acid from Pentasa During Normal and Accelerated Intestinal Transit Time. *Br J Clin Pharmacol* 1987; 3: 365-9.
181. Cheng Tong RL, Yun Mao, Tahseen Mirza, Raimar Lobenberg, Beverly Nickerson, Vivian Gray, , Wang Q. The Value of in Vitro Dissolution in Drug Development: A Position Paper from the Aaps in Vitro Release and Dissolution Focus Group. *Pharmaceutical Technology* 2009: 52-64.
182. Rojas Gomez R, Restrepo Valencia P. In Vitro-in Vivo Pharmacokinetic Correlation Model for Quality Assurance of Antiretroviral Drugs. *Colomb Med (Cali)* 2015; 3: 109-16.
183. Dressman JB, Reppas C. In Vitro-in Vivo Correlations for Lipophilic, Poorly Water-Soluble Drugs. *Eur J Pharm Sci* 2000: S73-80.
184. Patel N *et al*. Quantitative Prediction of Formulation-Specific Food Effects and Their Population Variability from in Vitro Data with the Physiologically-Based Adam Model: A Case Study Using the Bcs/Bddcs Class Ii Drug Nifedipine. *Eur J Pharm Sci* 2014: 240-9.
185. Shono Y *et al*. Forecasting in Vivo Oral Absorption and Food Effect of Micronized and Nanosized Aprepitant Formulations in Humans. *Eur J Pharm Biopharm* 2010; 1: 95-104.
186. Otsuka K *et al*. Coupling Biorelevant Dissolution Methods with Physiologically Based Pharmacokinetic Modelling to Forecast in-Vivo Performance of Solid Oral Dosage Forms. *J Pharm Pharmacol* 2013; 7: 937-52.
187. Schellekens RC *et al*. A Novel Dissolution Method Relevant to Intestinal Release Behaviour and Its Application in the Evaluation of Modified Release Mesalazine Products. *Eur J Pharm Sci* 2007; 1: 15-20.
188. Goyanes A *et al*. A Dynamic In vitro Model to Evaluate the Intestinal Release Behaviour of Modified-Release Corticosteroid Products. *Journal of Drug Delivery Science and Technology* 2015: 36-42.

189. Ahmed IS, Ayres JW. Comparison of in Vitro and in Vivo Performance of a Colonic Delivery System. *Int J Pharm* 2011; 1-2: 169-77.
190. Klein S *et al*. Site-Specific Delivery of Anti-Inflammatory Drugs in the Gastrointestinal Tract: An in-Vitro Release Model. *J Pharm Pharmacol* 2005; 6: 709-19.
191. Fadda HM *et al*. Physiological Bicarbonate Buffers: Stabilisation and Use as Dissolution Media for Modified Release Systems. *Int J Pharm* 2009; 1-2: 56-60.
192. Singh SK *et al*. A Novel Dissolution Method for Evaluation of Polysaccharide Based Colon Specific Delivery Systems: A Suitable Alternative to Animal Sacrifice. *Eur J Pharm Sci* 2015: 72-80.
193. Molly K *et al*. Development of a 5-Step Multi-Chamber Reactor as a Simulation of the Human Intestinal Microbial Ecosystem. *Applied Microbiology and Biotechnology* 1993; 2: 254-258.
194. Minekus M *et al*. A Computer-Controlled System to Simulate Conditions of the Large Intestine with Peristaltic Mixing, Water Absorption and Absorption of Fermentation Products. *Appl Microbiol Biotechnol* 1999; 1: 108-14.
195. Darwich AS *et al*. A Mechanistic Pharmacokinetic Model to Assess Modified Oral Drug Bioavailability Post Bariatric Surgery in Morbidly Obese Patients: Interplay between Cyp3a Gut Wall Metabolism, Permeability and Dissolution. *J Pharm Pharmacol* 2012; 7: 1008-24.
196. Darwich AS *et al*. Evaluation of an in Silico Pbpk Post-Bariatric Surgery Model through Simulating Oral Drug Bioavailability of Atorvastatin and Cyclosporine. *CPT Pharmacometrics Syst Pharmacol* 2013; 6: e47.

1285 Table 1: Gastrointestinal transit times in Ulcerative Colitis. Mean/Median (SD), rUC= UC patients in remission, aUC= active UC, dUC=distal UC, daUC=distal active UC,

1286 sUC=severe UC, drUC= distal UC in remission

Total gastrointestinal transit	**Gastric emptying time**	**Small intestinal transit time**	**Colorectal transit time**	**Proximal colon**	**Middle and distal colon**	**Orocecal transit time**	**Meal**	**Number of study subjects**	**Method**	**Reference**
sUC: 44.5h rUC: 51.8h Controls: 27.6h	sUC: 4.1h rUC: 3.4h Controls: 3.2h	sUC: 5.9h rUC: 6.2h Controls: 4.9h	sUC: 34.9h rUC: 43.3h Controls: 18.2h	sUC: 9.7h rUC: 7.0h Controls: 2.1h	sUC: 11.6h rUC: 18.0h Controls: 14.2h		Overnight fast, standardized breakfast, capsule swallowed afterwards	UC: 20 (relapse n=20, remission n=10) Controls: 20 (Previous study)	3D-Transit telemetric capsule system (diameter 8 mm, length 21 mm, density 1.6 g/cm^3)	Haase et al [23]
						UC: 2.04h (0.86) Controls: 1.51h (0.51)		UC: 95 Controls: 115	Lactulose breath test	Rana et al [29]
	UC: 10.59h (7.10) Controls: 5.19h (2.13)	UC: 8.03h (1.38) Controls: 7.38h (2.04)		UC: 12.66h (5.37) Controls: 30.68h (21.47)			Overnight fast, breakfast, SP swallowed	UC: 5 (mild to moderate) Controls: 5	SmartPill system	Bosworth et al [27]
		UC: 4.4h Non-IBD patients: 3.6h					Overnight fast, light breakfast 4h after swallowing the capsule	UC:23 aUC:20 rUC:3 Non-IBD patients: 125	Small capsule endoscopy studies	Fischer et al [30]
UC: 24h Controls: 26h							Overnight fast, capsule swallowed	UC: 5 (4 severe, 1 moderate) Controls: 15	Radiotelemetry capsule	Ewe et al [25]
		aUC: 7h (2.3) Controls: 6h (2.6)		aUC: 7h (5.5) Controls: 8h (9.2)	aUC: 12h (6.9) Controls: 7h (1.4)		Standardised ambulatory and dietary protocol	aUC: 4 Controls: 8	Radiotelemetry capsule	Nugent et al [28]
	UC: 1.6h	UC: 3.4h Controls: 3.2h (0.94)					Overnight fast, standarized breakfast, tablet swallowed afterwards	UC:6 (2 active, 4 quiescent)	Gamma scintigraphy of a radiolabelled tablet with cellulose acetate coating	Hardy et al [31] Controls: Davis et al [32]
	UC:2.7h (0.6)	UC:4.0h (1.5)					Light breakfast, tablet swallowed afterwards	UC:5	Gamma scintigraphy of a tablet containing compressed indium-111-labelled granules and coated with Eudragit L®	Hardy et al [33]
UC: 8h - >122.5h	UC: 1.05h (1.05)	UC: 8.93h (5.90)		UC: 2h - >97.7h			Overnight fast,swallowed capsule, fasting until capsule had passed the stomach	UC:6 (severe)	Fluoroscopic localization of capsule	Fallingborg et al [26]
aUC: 54.6h (21.8) rUC: 53.0h (32.6) daUC: 55.0h (22.0)	aUC: 0.81h (0.32) rUC: 0.88h (0.52) daUC: 0.96h (0.44) drUC: 1.13h (0.45)					aUC: 4.93h (0.95) rUC: 5.28h (1.33) daUC: 5.45h (1.28)	Radiolabelled meal	aUC: 15 rUC: 23 daUC: 23 drUC: 23	Hydrogen breath testing, radiolabelled meal and stool output	Rao and Read [24]

drUC: 60.5h (42.0) Controls: 48.8h (22.3)	Controls: 0.85h (0.37)					drUC: 5.23h (1.47) Controls: 3.82h (1.08)		Controls: 15		

1287

1288 Table 2: Colonic pH values in patients with ulcerative colitis. Mean/median (SD/range), treatment with [1]sulphasalazine, [2]mesalazine, [3]olsalazine, n=number of subjects

pH in controls	pH in patients with ulcerative colitis in remission	pH in patients with active ulcerative colitis	Special observations	Method	Reference
6.7(0.3) (n=7)	4.90(1.3)[1] 5.52(1.13)[2] 5.51(0.37)[3] (n=6)	4.7(0.72) (n=7)		Radiotelemetry capsule	Raimundo et al [38]
Caecum: 5.7 Rectum: 6.6 (n=39, previous study)		4.63 (1.93) (n=6, very active)	Very active disease: 2 patients transferred for surgery during the study, 1 patient died	Radiotelemetry capsule, fast of at least 8h until capsule passed the stomach	Fallingborg et al [26]
Right: 5.88 Left: 6.12 (n=12)	Right: 7.19 Left: 6.45 (n=4)	Right: 7 Left: 6.8 (n=7)		Radiotelemetry capsule, overnight fast until capsule passed the stomach	Press et al [36]
Right: 6.5 Left: 7 (n=15)		Right: 7.4 Left: 7.6 (n=5)	Lowest individual pH values were reached in the cecum (involved in two of five cases), pH did not fall under 5.5	Radiotelemetery capsule	Ewe et al [25]
Right: 6.5 (0.6) Left: 6.7 (0.1) (n=4)		Right: 6.7 (0.5) Left: 6.7 (0.9) (n=8)	In 2 patients with active distal UC a low pH < 5.5 was measured	Radiotelemetry capsule, standardised ambulatory and dietary protocol	Nugent et al [28]
Colon: 7.06 (0.41) (n=5)		Colon: 6.14 (0.37) (n=5, mild to moderate UC)		Smart Pill following a standardized egg sandwich meal and water	Bosworth et al [27]
Right: 7.8 (n=12)	Right: 6.5 (6.1–7.3) (n=12)	Right: 6.6 (5.5–7.7) (n=12)		Collection of the ascending colon fluid, measurement of pH	Vertzoni et al [37] Diakidou et al [39]

1289 Table 3: Gastrointestinal transit time in Crohn's disease. Mean/Median (SD), *controls in this study were patients with other diagnosis

Gastric emptying time	**Small intestinal transit time**	**Proximal colonic transit time**	**Orocecal transit time**	**Meal**	**Number of subjects**	**Method**	**Reference**
CD: 0.61h (0.75) controls*: 0.58h (0.29)	CD: 5.62h (0.78) controls*: 4.06h (1.39)			Overnight fast	CD:19 Patients with other diagnosis:178	Small capsule endoscopy studies	Niv et al [41]
	Active CD: 4.2h Inactive CD: 3.1h controls*: 3.6h			Overnight fast, light breakfast 4h after swallowing the capsule	Active CD: 33 Inactive CD: 22 Patients with other diagnosis: 125	Small capsule endoscopy studies	Fischer et al [30]
			CD: 2.32h (0.83) Controls: 1.51h (0.51)		CD:42 Controls:115	Lactulose breath test	Rana et al [29]
			CD: 2h controls: 1.47h		CD:45 Controls:20	Lactulose breath test	Tursi et al [42]
CD: 4.0h controls: 3.0h	CD: 2.4h controls: 3.0h	CD: 8.1h controls: 15.5h		Fed state	CD:6 Controls:8	Scintigraphy using a capsule containing ^{111}In-labelled pellets	Edsbacker et al [40]
CD: 3.2h (0.13) controls: 2.78h (0.11)				Fed state	CD (inactive): 26 Controls: 19	^{13}C octanoic acid breath test	Nobrega et al [46]
CD: 6.7h (4.2)	CD: 3.3h (1.7) (n=3)			Fed state	CD:5	Gamma scintigraphy of a tablet containing compressed	Hardy et al [33]

						indium-111-labelled granules and coated with Eudragit L®	

1290

1291 Table 4: Effect of IBD on drug interactions with gut bacterial enzymes. Data extracted from [11; 85-88]

Reaction	**Enzyme**	**Substrates**	**Bacteria with high enzymatic expression**	**Changes in IBD**
Azoreduction	Azoreductase	Sulfasalazine, prontosil, neoprontosil, balsalazine, olsalazine	*Clostridium sp.*	Azoreductase activity reduced in CD, *Clostridium* clusters IV and XIVa reduced in UC
Reduction	Nitroreductase	Nitrazepam	*Bacteroides fragilis/thetaiotamicron/vulgatus, Clostridium perfringens, Eubacterium limosum, Escherichia coli, Fusobacterium pseudonecrophorum, Peptostreptococcus asaccharolyticus*	*Bacteroides sp.* and *Eubacterium sp.* decreased
Deglucuronidation	β-glucuronidase	SN-38G (active metabolite of irinotecan)	*Bacteroides fragilis/thetaiotamicron/vulgatus, Clostridium barati/paraputrificum/perfringens, Eubactericum nitrogenes/aerofaciens, Peptostreptococcus asaccharolyticus*	*Bacteroides sp.* and *Eubacterium sp.* decreased
Thiazole ring-opening		Levamisole	*Bacteroides* and *Clostridium sp.* (Strongest metabolisers)	*Bacteroides sp.* and *Eubacterium sp.* decreased, *Clostridium* clusters IV and XIVa reduced in UC

1292

1293 Table 5: Gastrointestinal transit time in Celiac disease. Mean/Median (SD)

Gastric emptying time	Small intestinal transit time	Orocecal transit time	Meal	Number of study subjects	Method	Reference
Celiac disease (children):3.75h (1.12) (untreated), 1.46h (0.43) (treated) Controls: 2.02h (0.7)			Overnight fast, standard meal enriched with ^{13}C	Celiac disease: 9 Controls: 9	^{13}C-octanoic acid breath test	Perri et al [92]
Celiac disease: 5.43h Controls: 3.55h			Overnight fast, test meal	Celiac disease: 16 Controls: 24	Ultrasonographic emptying studies	Benini et al [98]
Celiac disease: 3.38h (0.53) Controls: 2.22h (0.25)			Overnight fast, test meal	Celiac disease: 9 Controls: 9	Ultrasonographic emptying studies	Bardella et al [99]
		Celiac disease (untreated): 4.05h (0.17) Controls: 1.95h (0.1)	Fasting period of at least 12h	Celiac disease: 16 Controls: 20	Hydrogen breath test	Battaglia et al [95]
		Celiac disease: 2.13h Controls: 1.01h	Overnight fast, test meal	Celiac disease: 25 Controls: 7	Hydrogen breath test	Spiller et al [96]
Celiac disease: 0.51h (0.37) Controls: 0.73h (0.81)	Celiac disease: 4.20h (1.12) Controls: 4.08h (1.47)		Bowel cleansing day before, fasting since midnight, drinking 2h/ eating 4h after capsule ingestions	Celiac disease: 30 Controls: 30	Small bowel PillCam®	Urgesi et al [100]

1294

Figure captions

Figure 1: Gastrointestinal pH profile in patients with Ulcerative Colitis (x: mean/median values, open circles: single values)

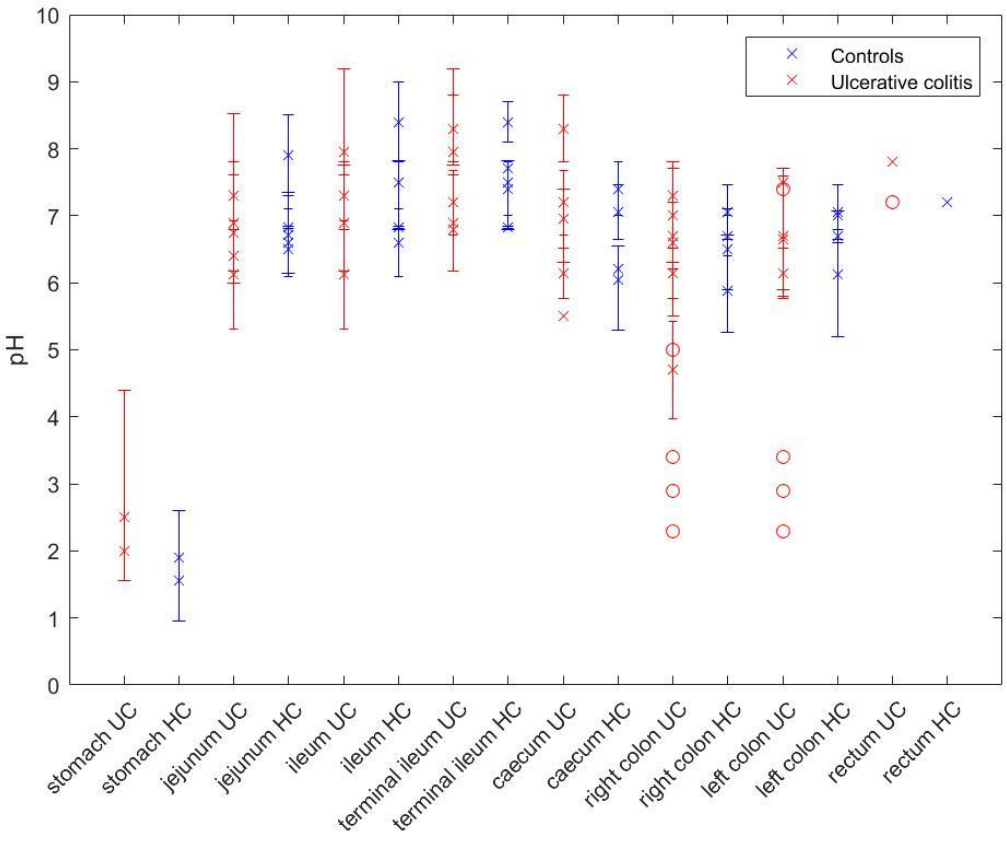
Figure 2: Gastrointestinal pH profile in Crohn's disease (x: mean/median values)

Figure 3: pH values in the small intestine of SBS patients (x: mean value, blue line: mean value controls, red line: mean value SBS patients)

Figure 4: Overview of changes in gastrointestinal diseases compared to healthy state

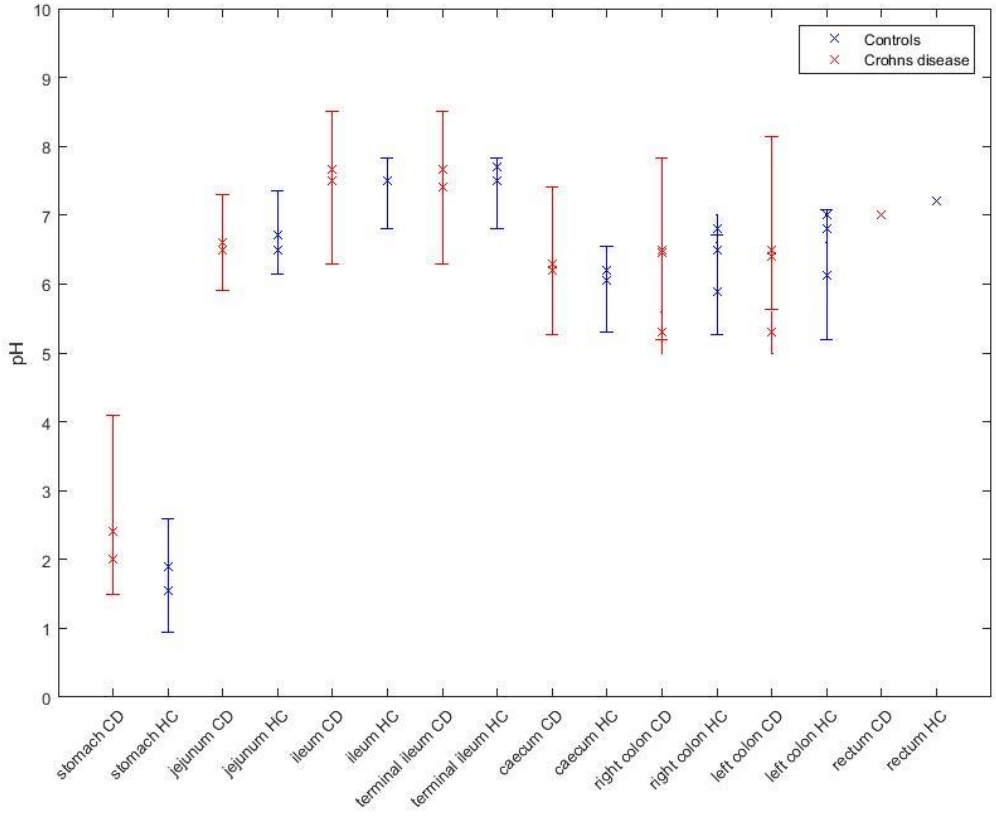
Figure 5: in vitro dissolution/release models for modified release dosage forms; a: Klein et al [190], b: Schellekens et al [187], c: Ahmed and Ayres [189], d: Goyanes et al [188]

1307



1308

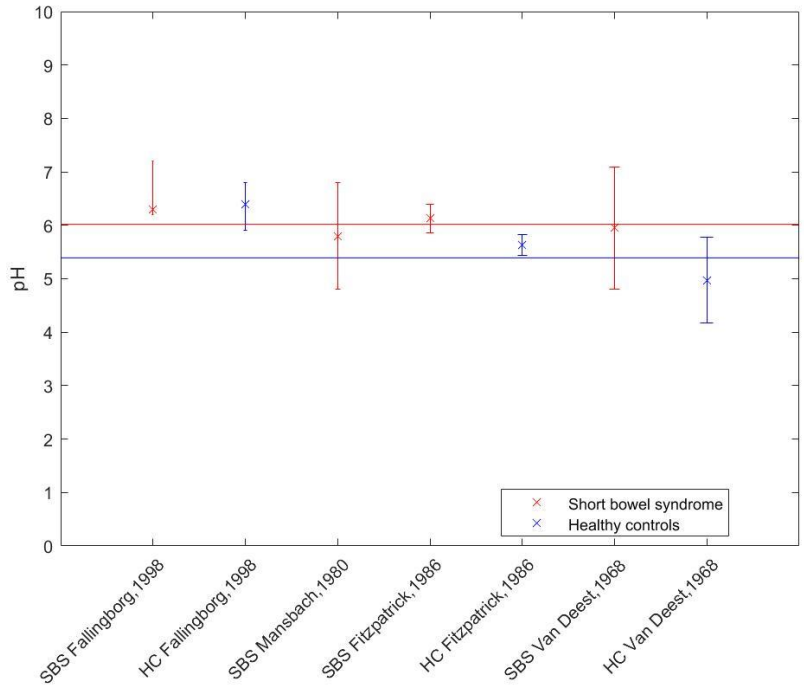
1309


Controls
Crohns disease
pH
0
1
2
3
4
5
6
7
8
9
10
stomach CD
stomach HC
jejunum CD
jejunum HC
ileum CD
ileum HC
terminal ileum CD
terminal ileum HC
caecum CD
caecum HC
right colon CD
right colon HC
left colon CD
left colon HC
rectum CD
rectum HC

1310

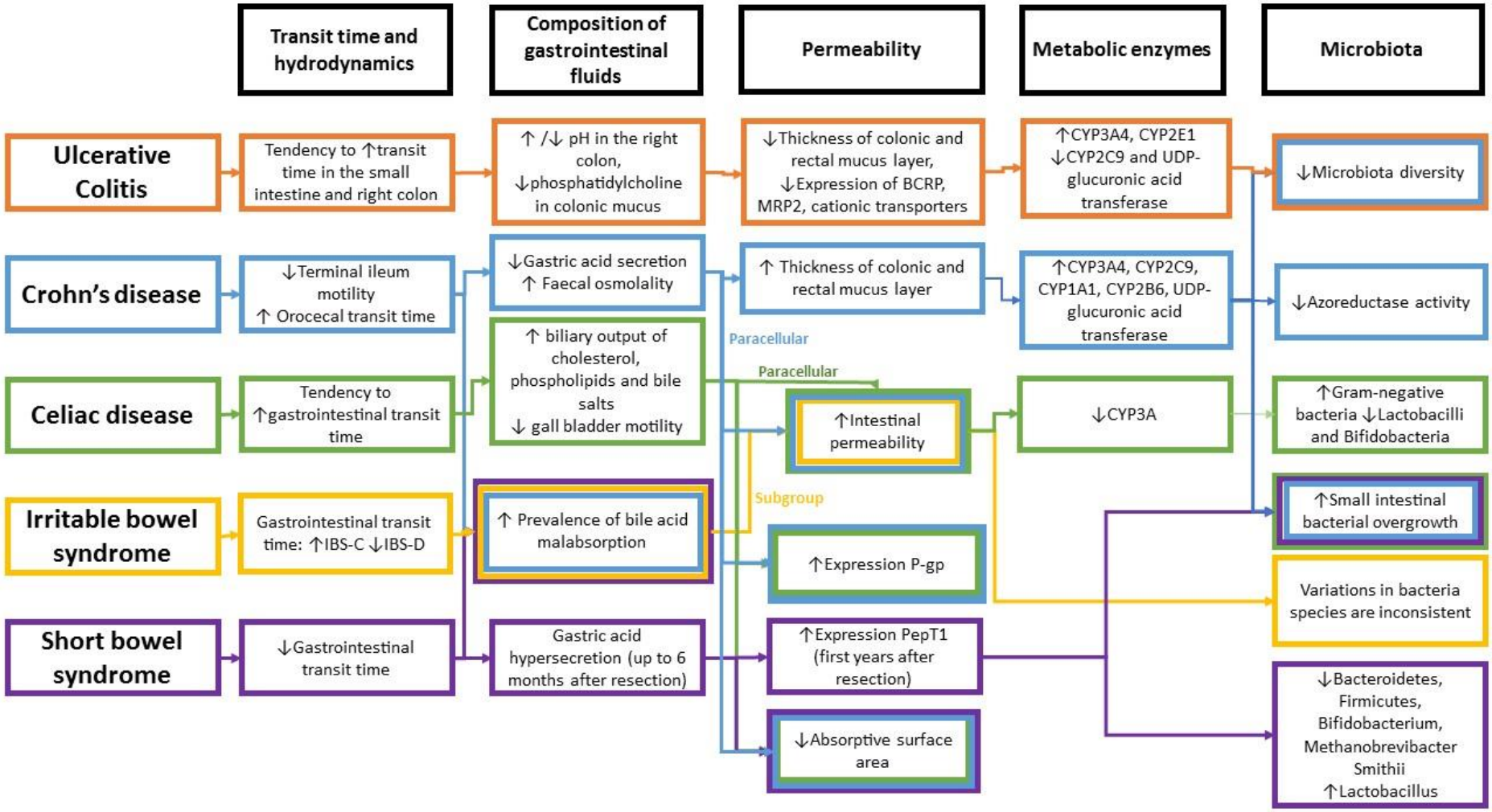
1311

1312



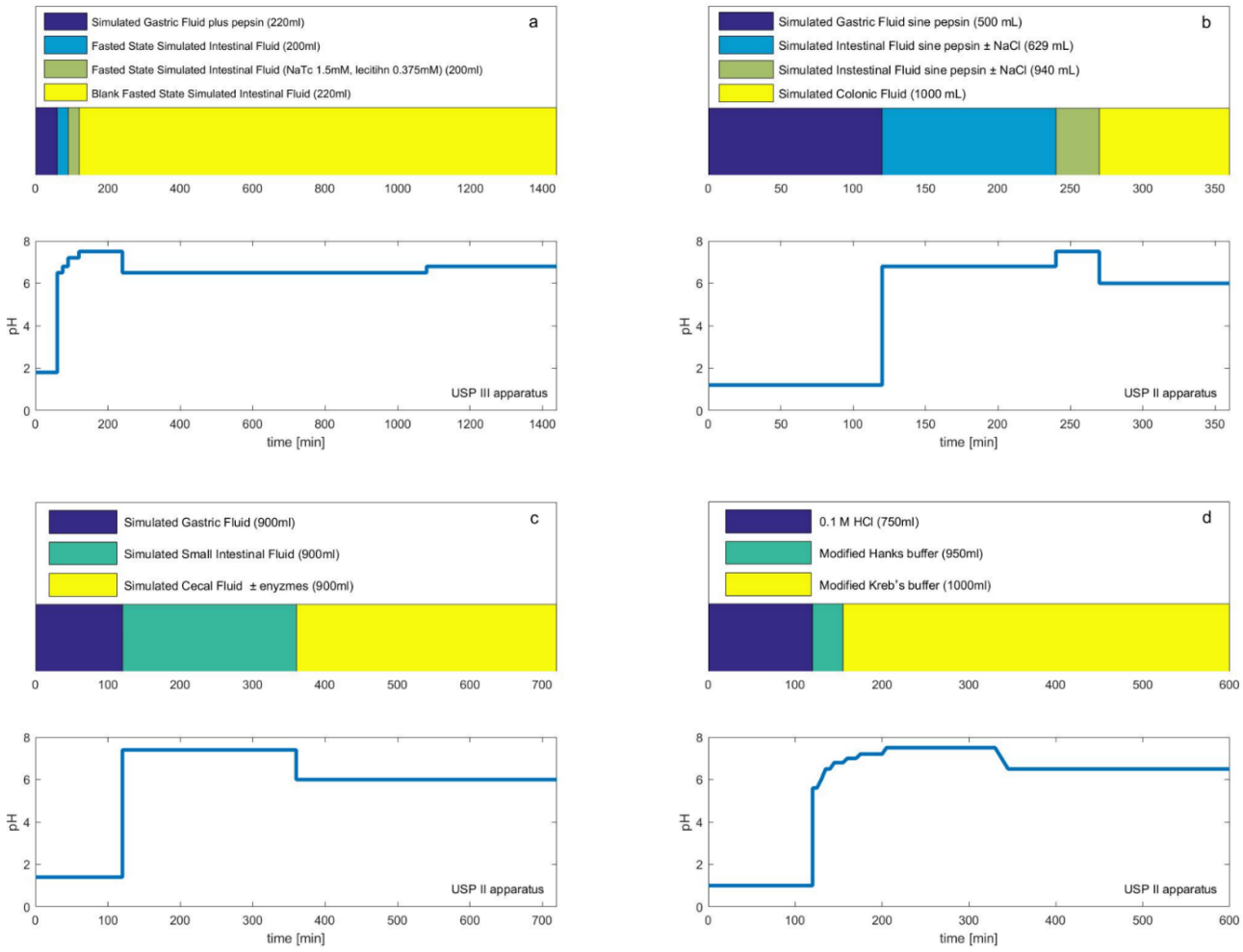
1313

1314


Transit time and hydrodynamics
Composition of gastrointestinal fluids
Permeability
Metabolic enzymes
Microbiota
Ulcerative Colitis
Tendency to ↑transit time in the small intestine and right colon
↑ /↓ pH in the right colon, ↓phosphatidylcholine in colonic mucus
↓Thickness of colonic and rectal mucus layer, ↓Expression of BCRP, MRP2, cationic transporters
↑CYP3A4, CYP2E1 ↓CYP2C9 and UDP-glucuronic acid transferase
↓Microbiota diversity
Crohn's disease
↓Terminal ileum motility ↑ Orocecal transit time
↓Gastric acid secretion ↑ Faecal osmolality
↑ Thickness of colonic and rectal mucus layer
↑CYP3A4, CYP2C9, CYP1A1, CYP2B6, UDP-glucuronic acid transferase
↓Azoreductase activity
Paracellular
Paracellular
Celiac disease
Tendency to ↑gastrointestinal transit time
↑ biliary output of cholesterol, phospholipids and bile salts ↓ gall bladder motility
↑Intestinal permeability
↓CYP3A
↑Gram-negative bacteria ↓Lactobacilli and Bifidobacteria
Subgroup
Irritable bowel syndrome
Gastrointestinal transit time: ↑IBS-C ↓IBS-D
↑ Prevalence of bile acid malabsorption
↑Expression P-gp
↑Small intestinal bacterial overgrowth
Variations in bacteria species are inconsistent
Short bowel syndrome
↓Gastrointestinal transit time
Gastric acid hypersecretion (up to 6 months after resection)
↑Expression PepT1 (first years after resection)
↓Absorptive surface area
↓Bacteroidetes, Firmicutes, Bifidobacterium, Methanobrevibacter Smithii ↑Lactobacillus

1315

1316


Simulated Gastric Fluid plus pepsin (220ml)
Fasted State Simulated Intestinal Fluid (200ml)
Fasted State Simulated Intestinal Fluid (NaTc 1.5mM, lecithin 0.375mM) (200ml)
Blank Fasted State Simulated Intestinal Fluid (220ml)
a
Simulated Gastric Fluid sine pepsin (500 mL)
Simulated Intestinal Fluid sine pepsin ± NaCl (629 mL)
Simulated Instestinal Fluid sine pepsin ± NaCl (940 mL)
Simulated Colonic Fluid (1000 mL)
b
Simulated Gastric Fluid (900ml)
Simulated Small Intestinal Fluid (900ml)
Simulated Cecal Fluid ± enyzmes (900ml)
c
0.1 M HCl (750ml)
Modified Hanks buffer (950ml)
Modified Kreb's buffer (1000ml)
d
pH
time [min]
USP III apparatus
USP II apparatus

1317